THE ARCHIVES

OF

INTERNAL MEDICINE

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago

RICHARD C. CABOT, Boston — GEORGE DOCK, New Orleans

DAVID L. EDSALL, Philadelphia — THEO. C. JANEWAY, New York

W. S. THAYER, Baltimore

VOLUME IV

1909

CHICAGO

AMERICAN MEDICAL ASSOCIATION

PUBLISHERS

CONTENTS OF VOLUME IV

JULY, 1909. NUMBER 1

PAGE.

HYPERALGESIA OF THE SKIN OVERLYING ACTIVE LESIONS IN PULMONARY TUBERCULOSIS. WILLIAM CHARLES WHITE, M.D., AND KARL H. VAN NORMAN, M.B. (TOR.), PITTSBURG, PA 1

THE PREVALENCE AND IMPORTANCE OF UNCINARIASIS AMONG APPARENTLY HEALTHY SOUTHERN-BRED WHITE MEN IN THE UNITED STATES ARMY. WESTON P. CHAMBERLAIN, M.D., JACKSON BARRACKS, LA 8

DISSEMINATED MILIARY TUBERCULOSIS OF THE SKIN. AN IMPORTANT SIGN IN GENERAL MILIARY TUBERCULOSIS OF INFANCY. WILDER TILESTON, M.D., BOSTON 21

SOME PROBLEMS IN IMMUNITY AND THE TREATMENT OF INFECTIOUS DISEASES. PHILIP HANSON HISS, JR., M.D., NEW YORK 32

THE CLOT CULTURE IN CONJUNCTION WITH THE AGGLUTINATION TEST IN TYPHOID. RANDOLPH LYONS, M.D., NEW ORLEANS 64

A MODIFICATION OF THE SAHLI BUTYROMETRIC TEST MEAL. J. C. FRIEDMAN, M.D., CHICAGO 69

A STUDY OF THE BLOOD IN PERTUSSIS. JOHN ALBERT KOLMER, M.D., PHILADELPHIA 81

BOOK REVIEW

DISEASES OF THE HEART. VON JÜRGENSEN, KREHL, VON SCHROTTER 97

AUGUST, 1909. NUMBER 2

SYSTEMIC BLASTOMYCOSIS. REPORT OF A CASE. BRYCE W. FONTAINE, M.D., MARCUS HAASE, M.D., AND ROBERT H. MITCHELL, M.D., MEMPHIS, TENN. 101

GLANDULAR FEVER. REPORT OF AN EPIDEMIC IN THE CHILDREN'S WARD OF THE UNION PROTESTANT INFIRMARY. J. EDWARD BURNS, M.D., BALTIMORE 118

THE ADMINISTRATION OF TUBERCULIN. E. C. L. MILLER, M.D., DETROIT 126

TESTS CONCERNING TUBERCLE BACILLI IN THE CIRCULATING BLOOD. E. C. SCHROEDER AND W. E. COTTON, BETHESDA, MD 133

THE RELAPSING FEVER OF PANAMA. SAMUEL T. DARLING, M.D., ANCON, CANAL ZONE 150

21175

PAGE.

REPORT OF A CASE OF STOKES-ADAMS DISEASE. THEODORE B. BARRINGER, JR., M.D., NEW YORK 186

BOOK REVIEW

A TREATISE ON DIAGNOSTIC METHODS OF EXAMINATION. SAHLI. KINNICUTT-POTTER 191

SEPTEMBER, 1909. NUMBER 3

THE EFFECTS OF CUTTING THE BRANCH OF THE HIS BUNDLE GOING TO THE LEFT VENTRICLE. LEWELLYS F. BARKER, M.D., AND A. D. HIRSCHFELDER, M.D., BALTIMORE 193

EXPERIMENTAL PAROTITIS. ISABELLA C. HEBB, M.D., CHICAGO 201

CERTAIN UNUSUAL LESIONS OF THE LYMPHATIC SYSTEM, INCLUDING A DESCRIPTION OF PRIMARY HODGKIN'S DISEASE OF THE SPLEEN AND A CASE OF GASTROINTESTINAL PSEUDOLEUKEMIA. DOUGLAS SYMMERS, NEW YORK. 218

SPHYGMOGRAPHIC STUDY OF A CASE OF COMPLETE HEART-BLOCK: A CONTRIBUTION TO THE STUDY OF THE ACTION OF STROPHANTHUS ON THE HUMAN HEART. GEORGE BACHMANN, M.D., PHILADELPHIA 238

EFFECTS OF THE ADMINISTRATION OR THE WITHHOLDING OF IODIN-CONTAINING COMPOUNDS IN NORMAL, COLLOID OR ACTIVELY HYPERPLASTIC (PARENCHYMATOUS) THYROIDS OF DOGS. SOME EXPERIMENTS ON (CONGENITAL) PRENATAL THYROID HYPERPLASIA IN DOGS: REMARKS ON THE CLINICAL MANIFESTATIONS ASSOCIATED WITH MARKED THYROID HYPERPLASIA. DAVID MARINE, M.D., AND C. H. LENHART, M.D., CLEVELAND, OHIO 253

OBSERVATIONS ON A CHILD WITH GASTRIC FISTULA IN RELATION TO RECENT ADVANCES IN THE PHYSIOLOGY OF GASTRIC SECRETION. R. S. LAVENSON, M.D., PHILADELPHIA 271

THE ABSENCE OF ADRENALIN IN MALIGNANT RENAL HYPERNEPHROMAS. JAMES R. GREER, M.D., AND GIDEON WELLS, M.D., CHICAGO 291

OCTOBER, 1909. NUMBER 4

FURTHER OBSERVATIONS ON THE THIRD HEART SOUND. WILLIAM SYDNEY THAYER, M.D., BALTIMORE 297

THE EFFECT OF TUBERCULOSIS ON THE HEART. F. M. POTTENGER, M.D., MONROVIA, CAL 306

INFLUENZAL MENINGITIS. DAVID J. DAVIS, M.D., CHICAGO 323

THE CLINICAL SIGNIFICANCE OF THE URINARY NITROGEN. III. NITROGENOUS METABOLISM IN TYPHOID FEVER. JAMES EWING AND C. G. L. WOLF, NEW YORK 330

CONTENTS OF VOLUME IV

PAGE.

A Study of the Mechanical Factors in Experimental Acute Pulmonary Edema. Joseph L. Miller, M.D., and S. A. Mathews, M.D., Chicago.. 356

A Comparative Study of Serum Diagnosis in Syphilis. Homer F. Swift, M.D., New York..... 376

The Much-Holzmann Serum Reaction in Insanity. A. J. Rosanoff, M.D., Kings Park, N. Y..... 405

NOVEMBER, 1909. NUMBER 5

Chronic Infectious Endocarditis. Frank Billings, M.D., Chicago..... 409

A Note on the Venous Pulse in Paroxysmal Tachycardia. Francis W. Peabody, M.D., Baltimore..... 432

Relation of Iodin to the Structure of Human Thyroids. Relation of Iodin and Histologic Structure to Diseases in General; to Exophthalmic Goiter; to Cretinism and Myxedema. David Marine, M.D., and C. H. Lenhart, M.D., Cleveland, Ohio..... 440

The Use of Active and Inactive Serum in the Complement Deviation Test for Syphilis. Homer F. Swift, M.D., New York..... 494

Ulceration of the Stomach and Necrosis of Salivary Glands Resulting from Experimental Injection of Bile Salts. Andrew Watson Sellards, M.D., Baltimore..... 502

The Effect of Hexamethylenamin on Guinea-Pigs. Channing Frothingham, Jr., M.D., Boston, Mass..... 510

DECEMBER, 1909. NUMBER 6

Results of Tuberculin Tests in Monkeys at the Philadelphia Zoological Gardens. C. Y. White, M.D., and Herbert Fox, M.D., Philadelphia 517

The Relation of Hypersusceptibility to Immunity. Paul A. Lewis, M.D., New York 528

Protein Metabolism in Typhoid Fever. Philip A. Shaffer, Ph.D., and Warren Coleman, M.D., with the Assistance of Michael Somogyi, E. A. Reinoso and Edna Cutler, New York..... 538

Gonococcemia, with a Report of Six Cases in which the Gonococcus Was Isolated from the Blood During Life. Ernest E. Irons, M.D., Chicago 601

Tubercle Bacilli in the Blood. Wilbur A. Sawyer, M.D., Berkeley, Cal. 628

HYPERALGESIA OF THE SKIN OVERLYING ACTIVE LESIONS IN PULMONARY TUBERCULOSIS

WILLIAM CHARLES WHITE, M.D.
AND
KARL H. VAN NORMAN, M.B. (Tor.).
PITTSBURG, PA.

In 1887 C. L. Dana,[1] in America, and in 1888 James Ross,[2] in England, published papers that were suggestive of a method of diagnosis which six years later Henry Head[3] made particularly valuable as an aid to the localization of visceral disease. Head with others had noticed that cutaneous tenderness accompanying certain diseases of the stomach was often confined to definite areas of the skin. He then undertook the study of involved areas in a number of cases of herpes zoster, hoping to throw light on the localization of skin tenderness in visceral disease. The post-mortem studies of these cases were carried on at times under great difficulty, but when finally the correlation of his work was accomplished he found that the areas involved in zoster corresponded to those of skin tenderness in visceral disease, and that these areas represented the nerve distribution of spinal cord segments.

The areas which he outlined for this segmental distribution of nerves and which are now so familiar as Head's diagrams in the present-day text-books differ from the areas later described by Sherrington[4] in the absence of overlapping, but the Sherrington areas represented those supplied by nerve roots while, as mentioned above, Head's areas represented the skin supplied by segments of the spinal cord. Head's areas also had reference to the sensations of pain, heat and cold rather than touch. In other words, Head showed that while there might be overlapping of nerve areas in the matter of touch sensation, there was no overlapping of skin nerve supply in the conducting of pain, heat and cold sensations.

Head concluded from these studies that there was a close central segmental association between the neurons supplying the viscera and the neurons conducting the sensations of pain, heat and cold from the skin. In explanation of the phenomenon of skin tenderness in visceral disease, he suggested that the sensations from the skin on reaching the cord en-

1. Dana, C. L.: New York Med. Jour., 1887, xlvi, 121.
2. Ross, James: Brain, London, 1888, x, 333.
3. Head, Henry: Brain, London, 1893, xvi, 1; 1894, xvii, 339; 1896, xix, 153.
4. Sherrington: Philo. Tr., London, B., 1898, exc, 45.

countered a condition of increased sensitiveness caused by the impressions arising from the diseased organ, and that this hypersensitive condition stimulated the transmission to the brain of an exaggerated impression of the sensation coming from the skin.

For the past year we have been interested in various complaints of pain and discomfort in the chest in patients who have been under our care in the hospital from time to time. These "pains" and hypersensitive conditions have frequently been used by us as confirmatory evidence of underlying pulmonary disease. At times it has been noticed that, for instance, the scraping of a cloth by accident across the nipple on one side has given rise to the sensation of pain; that occasionally a patient in scratching his skin has noticed an increased sensitiveness amounting at times to pain on one or the other side; or, again, that pressure over areas that from physical examination appeared to be actively diseased produced sensations of pain.

These facts stimulated us later to take up a more careful study of skin hyperalgesia in its relation to underlying pulmonary tuberculosis, and we found it confirmatory beyond our expectation of the evidence furnished by other methods of physical examination.

The tests were made with pin, test-tube of hot water and test-tube of cold water. In the tabulated cases von Pirquet's scarifier was used instead of an ordinary pin, because, the scarifier being longer than a pin, more even pressure could be exerted in drawing it across the skin; and also, as the scarifier was always of the same sharpness, the results to pain sense were more reliable. In the heat and cold tests ordinary test-tubes were filled with hot and cold water, corked and then used.

In order to eliminate the possibility of the nervousness of the patient, the tests were often made on the back first, the patient thus being unaware of the method and significance of the test. Also, in order to do away with the influence of the personal equation of the examiner, in other cases hyperalgesia was tested for the first step in the examination of the chest; i. e., before percussion, etc.

The table represents the results in 41 cases studied very carefully in every particular. Besides these we have verified the value of the test in 105 other cases.

In Case 37 both lungs are involved, but only the left is now active. While both lungs were active, hyperalgesia was present on both sides; but the disease is now arrested in the right lung and hyperalgesia is absent on the right side, but marked on the left side.

In Case 10 both lungs are involved, but the greatest involvement is in the right lung, whereas hyperalgesia is present on the left side. But

in the right lung there is cavity formation in the upper lobe, and doubtless there is a certain amount of fibrosis in the upper part of the lung. Hence there is really more activity in the left lung, over which hyperalgesia is present.

In Case 13 an acute pleurisy developed on two different occasions while we were studying hyperalgesia. On both occasions a series of tests failed to show any hyperalgesia over the seat of the pleurisy.

In three cases which have been under our observation since we have been making a close study of this phenomenon, we found marked hyperalgesia present over the lesion while active. As the lesion became less active hyperalgesia diminished, and finally with the arrest of the disease hyperalgesia totally disappeared.

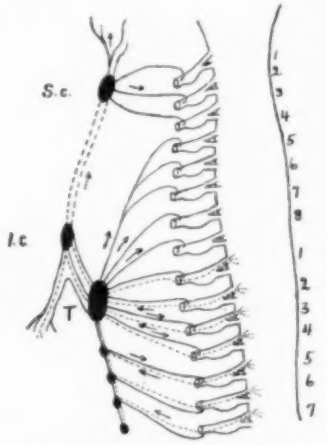


Fig. 1.—Schematic representation of the course of the sympathetic fibers arising from the thoracic region of the cord, illustrating connection between the sympathetic ganglia and the corresponding spinal root ganglia. (From Howell's "Text-Book of Physiology.") The preganglionic fiber is represented as a dotted line, the postganglionic as a heavy line. The arrows indicate the normal direction of the nerve impulses or nerve conductions. S.C. indicates the superior cervical ganglion; I. C., the inferior cervical ganglion; T., the first thoracic ganglion. The numerals indicate the corresponding spinal nerves. It will be noticed that the thoracic sympathetic system which joins with the vagus to supply the lungs gives off branches from its upper ganglia to the spinal root ganglia which supply the skin over the thorax.

Probably the most striking phenomenon of this study, apart from the hyperalgesia itself, was the localization of the hyperalgesia to the skin directly overlying the active lesion in the lung. This corresponds to the findings of other observers with this method of studying disease of the

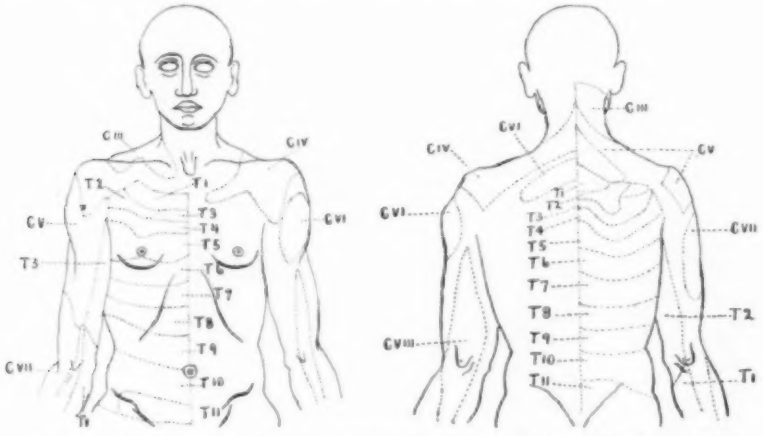
TABLE SHOWING RELATION BETWEEN ACTIVE INVOLVEMENT OF LUNG AND SKIN HYPERALGESIA

Case.	Involvement.		Involvement Extent.				Lung Most Active.	Active Involvement.		Hyperalgesia.			Hyperalgesia Extent.				Hyperalgesia Most Marked		Hyperalgesia Present to		
			Left Lung.		Right Lung.								Left Side.		Right Side.						
	L. Lung.	R. Lung.	Ant.	Post.	Ant.	Post.		L. Lung.	R. Lung.	Slight.	Moderate.	Marked.	Ant.	Post.	Ant.	Post.	On Left Side.	On Right Side.	Pin.	Hot Water.	Cold Water.
1	+	+	5th rib...	9th rib...	3d rib.....	6th I. S..	L.....	+	....	—	—	+	5th rib...	9th rib...	.....	.....	....	....	+	+	+
2	+	+	2d I. S...	5th I. S..	3d rib.....	6th I. S..	R.....	+	+	—	+	—	.....	.....	3d rib....	7th rib....	....	....	+	+	+
3	—	+	.....	.....	2d rib.....	5th I. S..	R.....	—	+	—	—	+	.....	.....	2d rib....	5th I. S....	....	....	+	+	+
4	+	+	2d rib....	4th rib...	3d rib.....	5th rib...	R.....	+	+	—	+	—	2d rib....	4th I. S..	3d rib....	5th rib....	....	....	?	+	+
5	+	+	1st I. S..	3d rib....	1st I. S....	3d rib....	R. and L.	+	+	+	—	—	.....	.....	2d rib....	3d rib.....	....	....	+	+	+
6	+	+	3d rib....	All.....	3d I. S.....	7th rib...	R. and L.	+	+	—	+	—	3d I. S...	5th rib...	3d I. S...	5th rib....	....	....	+	+	+
7	+	+	5th I. S..	All.....	3d rib.....	7th rib..	L.....	+	+	—	—	+	4th rib...	7th rib...	.....	.....	....	....	+	+	+
8	+	+	All.....	All.....	All.....	All.....	L.....	+	+	—	—	+	All.....	All.....	Slight....	Slight.....	+	—	+	+	+
9	+	+	2d rib..	4th I S..	All.....	All.....	R.....	+	+	—	—	+	.....	.....	All.....	All.....	....	....	+	+	+
10	+	+	2d I. S...	5th rib...	3d rib.....	7th rib...	R.....	+	+	+	—	—	2d I. S..	5th I. S..	.....	.....	....	....	+	+	+
11	+	+	All.....	All.....	All.....	All.....	R. and L.	+	+	—	+	—	3d rib....	5th I. S..	3d rib. ..	4th I. S....	+	—	+	+	+
12	+	+	4th rib...	7th rib...	3d I. S.....	8th I. S..	R.....	+	+	—	+	—	.....	.....	4th rib...	5th I. S....	....	....	+	+	+
13	+	+	All.....	All.....	2d rib.....	3d rib...	L.....	+	—	—	—	+	3d I. S..	8th I. S..	.....	.....	....	....	+	+	+
14	+	+	2d I. S...	3d rib....	3d rib.....	5th I. S..	R.....	—	+	—	+	—	Clavicle	3d rib....	2d rib....	3d rib.....	—	+	+	+	+
15	+	+	1st I. S..	3d rib....	3d rib.....	6th rib...	R.....	—	+	—	+	—	Clavicle	3d rib....	3d rib....	All.....	—	+	+	+	+
16	+	+	2d I. S...	6th rib...	3d rib.....	7th rib...	L.....	+	+	+	—	—	2d rib....	.....	.....	.....	....	....	+	+	+

17	+	+	2d rib.	5th rib.	2d I. S.	5th rib.		—	—	+	—	—	2d rib.	5th rib.					+	+	+
18	+	+	2d rib.	6th rib.	3d rib.	5th rib.		—	—	—	+	—	3d rib.	5th I. S.	4th rib.	3d rib.			+	+	+
19	+	+	2d rib.	3d rib.	3d rib.	6th rib.	R.	+	+	+	—	—	2d rib.	3d rib.	2d rib.	3d rib.			+	+	+
20	—	+			3d rib.	5th I. S.	R.	—	+	—	—	+			3d rib.	5th rib.			+	+	+
21	+	+	4th rib.	8th I. S.	1st I. S.	2d rib.	L.	+	+	—	—	+	4th rib.	8th rib.	Apex	Apex	+	—	+	+	+
22	+	+	4th rib.	7th rib.	3d I. S.	7th rib.	L.	+	+	—	—	+	4th rib.	All.	Slight.	Slight.	+	—	+	+	+
23	+	+	3d I. S.	4th rib.	2d rib.	4th rib.	L.	+	+	—	—	+	3d rib.	4th rib.	3d rib.	4th rib.	+	—	+	+	+
24	+	+	4th rib.	8th rib.	3d I. S.	6th I. S.	L.	+	+	—	—	+	4th rib.	8th rib.	3d I. S.	6th I. S.	+	—	+	+	+
25	+	+	5th rib.	7th rib.	4th rib.	6th rib.	R. and L.	+	+	—	—	+	4th rib.	7th rib.	4th rib.	6th rib.	—	+	+	+	+
26	+	+	All.	All.	All.	All.	R.	+	+	—	—	+	Slight.	Slight.	All.	All.			+	+	+
27	+	+	3d rib.	6th rib.	2d rib.	3d I. S.	R.	+	+	—	—	+	4th rib.	6th rib.	2d rib.	3d I. S.	+	—	+	+	+
28	—	+			1st I. S.	3d rib.	R.	—	+	—	+	—			1st I. S.	3d rib.			+	+	+
29	+	+	4th rib.	4th I. S	3d rib.	8th rib.	R.	—	+	—	—	+			3d rib.	8th rib.			+	+	+
30	+	+	4th rib.	5th rib.	3d rib.	3d rib.	R.	—	+	+	—	—			2d I. S.	3d rib.			+	+	+
31	+	+	3d I. S.	6th I. S.	All.	All.	R.	+	+	—	—	+	Slight.	Slight.	All.	All.	—	+	+	+	+
32	+	+	All.	All.	3d rib.	7th rib.	L.	+	+	—	—	+	All.	All.	4th rib.	6th rib.	+	—	+	+	+
33	+	+	3d rib.	4th rib.	All.	All.	R.	+	+	—	—	+	Slight.	Slight.	All.	All.	—	+	+	+	+
34	+	+	2d I. S.	7th rib.	2d I. S.	4th I. S.	L.	+	+	+	—	—	2d I. S.	6th rib.					—	+	+
35	+	+	4th rib.	7th rib.	3d I. S.	3d I. S.	L.	+	+	—	—	+	4th rib.	6th rib.					+	+	+
36	+	+	4th rib.	7th rib.	4th rib.	8th rib.	R.	+	+	-	+	—		7th rib.	4th rib.		—	+	+	+	+
37	+	+	All.	All.	2d I. S.	5th rib.	L.	+	—	—	—	+	4th I. S.	8th rib.					+	+	+
38	—	+			3d rib.	6th rib.	R.	—	+	—	—	+			3d rib.	6th rib.			+	+	+
39	+	+	2d I. S.	5th rib.	3d rib.	5th rib.	R.	—	+	—	—	+			3d rib.	5th rib.			+	+	+
40	—	+			Lower lobe.	Lower lobe.	R.	—	+	—	—	+			Lower lobe.	Lower lobe.			+	+	+
41	+	—	2d I. S.	5th rib.			L.	+	—	—	+	—	2d I. S.	5th rib.					+	+	+

abdominal organs in which the hyperalgesia is confined to the skin over the lesion in these organs. In both instances the conclusion from the results is that the distribution of the hyperalgesia has no definite relation to the spinal nerve distribution, but rather to some existing central correlation between the nerve supply of the organ and the nerve supply of the skin overlying that organ. In other words, the results correspond to and confirm what Head describes as segmental distribution.

So far as anatomic study has led us, there is no evidence that any branches of the posterior roots of the spinal nerves enter the nerve supply to the lungs. This itself, if true, would preclude a possibility of the distribution of the hyperalgesia corresponding to the spinal nerve distribution. Of course, if the hyperalgesia corresponded to the spinal nerve



Figs. 2 and 3.—Areas of pain sensation in visceral disease; diagram (after Henry Head) showing the areas of skin supplied by the spinal root ganglia which are involved in hyperalgesia as described in this paper. (From Barker's "The Nervous System.")

supply, one would expect to find the disturbance of pain, heat and cold sensations projected beyond the lesion to the limits of the supply of the nerves involved, which was never found to be the case.

On the other hand, the accompanying diagrams (Figs. 1, 2 and 3) will show that there is a definite connection existing between the sympathetic system which supplies the internal organs and the spinal root ganglia containing the cells which send processes to the skin for the conducting of sensations from this tissue. So far as we know, this is the only connection that exists, or at least the only likely connection, as any

other connection must be a central one from high up in the nervous system at the center of origin of the vagus nerve which forms the other definite nerve supply of the internal organs.

This nerve supply does not, of course, refer to the pleura, which has a definite supply to its parietal portion from the intercostal nerves. But we have convinced ourselves from a limited number of cases that the hyperalgesia has no relation to pleural lesions, as, for instance, in Case 13, in which there is no hyperalgesia over an acute pleural involvement.

The only explanation of the phenomenon of skin hyperalgesia following lesions of the internal organs which we have to offer is that presented by Head. It will be readily understood by reference to the diagrams (Figs. 2 and 3). Evidently the disturbance is a cell condition from the fact that the hyperalgesia is so closely limited to the skin overlying the diseased area beneath. Probably the area of disease provides an irritation to the fibers of the sympathetic supplying that area which in turn transmits impulses through those branches which connect the sympathetic system with the spinal ganglia to cells in the spinal ganglia which send processes to the skin overlying the lesion. These impulses probably increase the sensitiveness of these cells to such a degree that impressions coming to them from the skin are increased in severity and are thus transmitted to the brain as exaggerated sensations.

The hyperalgesia of skin differs markedly from the sensation of pain or soreness on deep pressure which has been emphasized by K. Francke,[5] and which has been noticed and used by ourselves frequently as an aid to diagnosis in underlying active tuberculous lesions. One feels that this sensation of soreness on deep pressure has a different origin from hyperalgesia, and is probably due to an extension of the inflammatory changes surrounding a tuberculous lesion to the pleura and overlying muscles.

CONCLUSIONS

1. Hyperalgesia of the skin to pain, heat and cold sensations is present over active tuberculous involvement of the lungs.

2. It has a very definite distribution, corresponding very closely to the limits of active involvement in the lungs.

3. With the arrest of activity hyperalgesia disappears.

4. Hyperalgesia depends on involvement of the lung and not of the pleura.

We desire to express our thanks to Dr. Alfred K. Haywood for his assistance in this work.

5. Francke, K.: Beitr. z. klin. d. Tuberk., 1908, x, 225.

THE PREVALENCE AND IMPORTANCE OF UNCINARIASIS AMONG APPARENTLY HEALTHY SOUTHERN-BRED WHITE MEN IN THE UNITED STATES ARMY *

WESTON P. CHAMBERLAIN, M.D.
JACKSON BARRACKS, LA.

Until very recently the prevalence of hookworm disease among soldiers who have always resided in the United States appears to have been very little investigated. The only mention of uncinariasis in the report of the Surgeon-General of the Army for 1908 is that an examination of the stools of 21 soldiers at Fort Root, who had recently returned from the Philippine Islands, showed all to contain ova of *Ankylostoma duodenale*. In 1904 the surgeon at Fort Porter, New York, reported the presence of ankylostoma in many cases admitted to hospital for other conditions; but where the infection probably originated is not stated in the reference to his work. On Dec. 7, 1908, Captain J. F. Siler, of the Medical Corps of the Army, stationed at the large recruit depot of Fort Slocum, New York, reported to the Surgeon-General that of 19 southern recruits examined, 16, or 84 per cent., harbored ankylostoma. Of these, 3 were suspected of being so infected, while the remainder were in hospital for other reasons.

As a result of Dr. Siler's work, instructions were sent out for army surgeons to investigate the prevalence of uncinariasis among southern-bred soldiers.[1] The result of my work on this subject illustrates how a well-known condition may be entirely overlooked until one's mind is specially directed to it. Prior to the present investigation, no case of uncinariasis had ever been recorded on the sick report at Jackson Barracks. During the three years I have been stationed there two cases were suspected of ankylostomiasis, but on examination both proved negative. Yet the result of my recent work is to show that 25 per cent. of the entire command harbored the hookworm, and that the condition had been

---

*Read at the sixth annual meeting of the American Society of Tropical Medicine, held at the U. S. Naval Medical School, Washington, D. C., April 10, 1909.

1. By "southern-bred" is meant in this article men who were born and always had lived in some one of the following states: Maryland, Virginia, West Virginia, North Carolina, South Carolina, Georgia, Florida, Alabama, Mississippi, Louisiana, Texas, Kentucky, Tennessee, Arkansas and Missouri.

wholly unsuspected. It is undoubtedly true that similar mild infections are being constantly overlooked throughout the southern states as well as in the army.

PERCENTAGE OF MEN INFECTED

The work at Jackson Barracks has consisted of the examination of the blood and stools of 147 apparently healthy soldiers. For analysis these 147 cases are separated into four classes. The details are given in appended tables.

Class 1.—Newly enlisted southern-bred recruits received at the recruit depot at Jackson Barracks. There were 43 of these, and 29 were infected with uncinaria, a percentage of 67 (Table 1).

Class 2.—Southern-bred soldiers in the permanent command at Jackson Barracks serving in their first enlistment; that is, having three years or less in the army. Fifty-seven of these were examined and 31 were found infected, a percentage of 54. The average length of service for these men was 1.1 years, and only a single one of the positive cases had been in the army over two years (Table 2).

Class 3.—Southern-bred soldiers in the permanent command at Jackson Barracks who have served more than one enlistment; that is, over three years. There were 33 of these examined, and only 4 were found to have uncinariasis, a percentage of 11. The average length of service for these men was 6.4 years. The four men infected had served, respectively, 4, 5, 6½ and 7 years. The number of worms found in these cases was small, the average being 5½ per man (Table 3).

Class 4.—Soldiers and recruits at Jackson Barracks who had lived little or not at all in the south. Fourteen of these were examined, and no ova of uncinaria were found nor did the eosinophile count of any suggest the presence of intestinal parasites.

If the new recruits (Class 1) and the soldiers in their first enlistment (Class 2) are combined, we have 100 southern-bred soldiers with less than three years' service among them among whom an even 60 per cent. were infected with hookworms. Adding the 4 positive cases among the older soldiers, gives in all 64 cases of uncinariasis to be studied.

That this high percentage of uncinaria infections among southern-bred recruits is probably the rule rather than the exception is shown by the following reports: Captain P. J. Owen, Medical Corps, U. S. A., stationed at Columbus Barracks, Ohio, records the finding of 8 cases of infection with *Uncinaria americana* among southern recruits, though how many were examined in all is not stated. Captain Siler has recently written me that he has now examined 140 recruits, finding over 85 per

TABLE I.—FORTY-THREE UNSELECTED SOUTHERN-BRED RECRUITS EXAMINED AT JACKSON BARRACKS, LA.*

Case No.	Age.	Height, inches.	Weight before treatment.	Weight after treatment.	Occupation at time of enlistment.	Occupation previous to enlistment.	Birthplace.	Residence.	History of ground itch.	Years since ground itch.	Color.	% hemoglobin	% Polymorphonuclears.	% eosinophiles.	% lymphocytes, small	% lymphocytes, large.	% transitionals.	% mast cells.	Number of ova found in stool.	Number of worms found after treatment.	Remarks.
1	22	66	124	133	Farmer	Farmer	Miss.	Miss.	N	....	Good	100	62	6.5	22	7	2.5	0	Many	18	
2	21	68	133	140	Farmer	Farmer	Miss.	Miss.	P	12	Good	100	66.5	8.5	16.5	5.5	2	1	Many	42	
3	23	69	135	135	Plumber	None	S. C.	Ala	P	14	Pale	80	74.5	2	15	3.5	5	0	Few	0	
4	18	66	127	124	Factory	Farmer	Miss.	N. C.	P	14	Good	100	44	26	22	4	4	0	Few	3	
5	24	68	145	152	Farmer	Farmer	Miss.	Miss.	P	14	Pale	80	46	7	26	11.5	9.5	0	Few	17	
6	21	69	127	....	Solicitor	Engineer	Ala	Ala	N	....	....	....	35.5	7	44.5	9	3.5	0.5	0	.....	Never lived in country.
7	19	66	118	....	Laborer	Laborer	Miss.	Miss.	?	....	Good	90	40	20.5	25.5	4	5	0	Very few	.....	Left before treatment.
8	23	68	128	129	Collector	Farmer	Ga.	La.	P	15	Good	90	60.5	7.5	20	7	4.5	0.5	.....	33	Farmer 6 years ago.
9	20	66	126	129	Lumber	Farmer	Tex.	Miss.	P	9	Good	90	63	11	17	6	3	0	Many	10	
10	28	68	153	159	Engineer	Farmer	Ala	Miss.	P	20	Good	80	47	8.5	32	7	5.5	0	Very few	2	Farmer 6 years ago.
11	22	69	144	154	Farmer	Farmer	Ala	Ala	P	12	Fair	80	69	7	15.5	4	3.5	1	Very many	12	
12	27	66	130	....	Carpenter	Farmer	Miss.	Miss.	P	18	Pale	90	62.5	15	9.5	3.5	9	0.5	Few	5	
13	23	65	128	....	Sawmill	Farmer	Miss.	Miss.	N	....	Good	90	65	1.5	20	8.5	4.5	0.5	0	.....	Not on farm for 11 years.
14	23	72	151	....	Barber	Farmer	Fla	La.	P	7	Fair	80	51.5	17	23	2.5	5	1	Very many	.....	Left before treatment.
15	18	67	150	159	Laborer	Farmer	W. Va.	La.	N	....	Pale	90	49	11	28.5	5.5	5	1	Very few	0	
16	26	67	129	139	Laborer	Farmer	Ala	Ala	P	20	Good	90	68	5	23	2.5	1.5	0	Few	1	
17	29	69	152	....	Factory	Farmer	Ala	Ala	P	5	Pale	90	71.5	4.5	18	3	2	1	Few	.....	Left before treatment.
18	23	72	150	154	Farmer	Farmer	Ga.	Ga.	P	15	Good	80	65	10.5	14	3.5	6.5	0.5	Very many	0	
19	31	70	190	....	Carpenter	Butcher	Ga.	Ga.	P	4	Good	100	56	2.5	34.5	4.5	2.5	0	0	.....	
20	23	72	147	157	Stable	Farmer	Ala	Ala	P	12	Pale	100	68	4	20	6	2	0	Very many	2	
21	25	65	124	....	Cooper	Farmer	La.	La.	P	15	Good	100	50	2	39.5	5.5	3	0	0	.....	

22	21	64	126	126	Machinist	Farmer	La.	La.	P	12	Good..	100	58.5	5.5	29	4.5	2.5	0	Very few	16	
23	22	70	152	147	Machinist	Farmer	N. C...	Pana...	N	....	Xlnt...	100	60	7	25	5	2	1	Many....	1	
24	24	69	133	....	Showman	Farmer	Pa.	Ala	N	....	Fair..	90	75	2	17	4	2	0	0	.....	Not on farm for 12 years.
25	27	71	150	149	Laborer	Farmer	Tex.	Tex.	N	....	Good ..	90	31	5	50	7.5	6.5	0	Many....	24	
26	21	69	157	159	Farmer	Logging	Miss.	Miss.	P	8	Good..	100	68.5	8.5	16.5	3.5	2.5	0.5	Few.....	1	
27	33	71	156	....	Lumberman	Farmer	Tex.	Miss.	N	....	Pale...	100	75	0	18	5	2	0	0	.....	
28	21	71	154	....	Millman	Farmer	N. C...	Miss.	P	10	Good..	90	50	23	15	8	4	0	Few.....	.....	Left before treatment.
29	21	67	140	....	Farmer	Farmer	Miss ..	Miss.	N	....	Pale...	90	62	3	27	4	4	0	0	.....	
30	22	64	122	....	Laborer	Millman	La.	La.	N	....	Good..	90	61	1	29	2.5	5	1.5	.....	.....	Never lived in country.
31	19	70	149	153	Laborer	Farmer	Miss.	Miss.	N	....	Good..	90	73	6	13	5	3	0	Very many	5	
32	23	70	157	163	Farmer	Farmer	La.	La.	N	....	Good..	90	54	26	13	3	2	2	Very few	7	
33	23	69	138	146	Farmer	Farmer	N. C...	N. C...	P	14	Good..	100	46	10	28	9	5	2	Few.....	19	
34	18	69	125	135	Farmer	Farmer	Ala	Ala	N	....	Fair...	90	40	10.5	35.5	8	5.5	0.5	Very many	11	
35	21	68	129	130	Laborer	Farmer	La.	La.	N	....	Good..	90	35.5	7	32.5	11.5	18.5	0	Very many	75	
36	27	69	140	....	Fireman	Fireman	La.	La.	N	....	Good..	80	70	3	22.5	1.5	3	0	0	.....	Never lived out of N. O., La.
37	25	69	137	....	Tinner	Motorman	La.	La.	N	....	Good..	....	72	0	21	4	3	0	0	.....	Never lived in country.
38	29	71	150	157	Laborer	Laborer	La.	La.	N	....	Good..	100	56	1	36	3	3	1	0	.....	Never lived out of N. O., La.
39	26	75	148	....	Carpentry	Farmer	N. C...	La.	N	....	Good..	100	49.5	4.5	39	2	4	1	0	.....	
40	22	71	186	191	Pile Driver	Teamster	Tex.	La.	N	....	Xlnt...	90	71.5	4.5	17	5	2	0	0	.....	
41	27	67	148	141	Farmer	Farmer	Md	Md	N	....	Good..	90	70	6	14	4	6	0	Very few	1	
42	22	67	138	145	Showman	Farmer	Ky.	Ala	N	....	Pale...	100	65	2	22	5	6	0	Very few	1	Farmed in Ky. 10 years ago.
43	28	64	120	....	Sawmill	Farmer	Md	Ala	N	....	Good..	80	76	2	13.5	5.5	2.5	0.5	0	.....	Farmed in Md. 7 years ago.

Twenty-nine cases of uncinariasis out of 43 = 67 per cent.
Average eosinophilia for positive cases, 9.9 per cent.
Average eosinophilia for negative cases, 2.4 per cent.
Average weight for positive cases, 140.2 lbs.
Average weight for negative cases, 142.9 lbs.
Average gain in weight after treatment, 3.4 lbs.

* N means negative history for ground-itch; P means positive history for ground-itch; Xlnt means "excellent."

TABLE II.—FIFTY-SEVEN UNSELECTED SOUTHERN-BRED SOLDIERS IN THEIR FIRST ENLISTMENT PERIOD (THREE YEARS) *

Case No.	Age.	Years in Army.	Height, inches.	Weight before treatment.	Weight after treatment.	Occupation at time of enlistment.	Occupation previous to enlistment.	Birthplace.	Residence.	History of ground itch.	Years since ground itch.	Color.	% hemoglobin.	% polynuclears.	% eosinophiles.	% lymphocytes, small.	% lymphocytes, large.	% transitionals.	% mast cells.	Number of ova found in stool.	Number of worms found after treatment.	Remarks.
44	34	¼	64	140	....	Mechanic	Cook	Ga.	Ga.	N	....	Good.	90	76	3.5	16	3	1.5	0	0	.....	Never lived in country.
45	23	1	68	143	146	Fireman	Fireman	Miss.	Miss.	N	....	Good.	90	56	4	31	7	2	0	Many	2	Never lived in country.
46	22	1	68	151	....	Student	Farmer.	Miss.	Miss.	P	10	Good.	90	68	3	20	5	3	1	0	.....	
47	21	1	67	126	135	Farmer.	R. R. Laborer	Miss.	Miss.	P	7	Pale	80	63	7.5	24	2.5	3	0	Very many	82	
48	23	1	69	166	167	Fireman	Farmer.	Miss.	Miss.	P	10	Pale	100	64	6	23	4	3	0	Many	35	
49	22	½	72	146	....	Machinist	Machinist.	Miss	Va.	N	....	Good.	100	60	2	28	3	7	0	0	.....	
50	29	¾	70	146	....	Engineer	Farmer.	Ala.	Miss.	P	7	Good.	90	53.5	7.5	29.5	4	5.5	0	Very few	2	
51	19	1	65	145	138	Farmer.	Farmer.	Ala.	Miss.	P	8	Good.	90	42.5	8	37	7.5	4	1	Many	35	
52	22	¾	66	115	124	Farmer.	Farmer.	Ala.	Miss.	N	....	Good.	90	46	12	32.5	6.5	2.5	0.5	Very many	13	
53	26	1¼	69	140	140	Laborer	Farmer.	Ala.	Miss.	P	12	Good.	100	58	4	36	1	1	0	Very few	3	
54	20	¾	68	144	132	Smith	Smith.	Miss.	Miss.	N	....	Good.	100	62.5	4.5	26.5	2.5	3.5	0.5	Few	4	
55	14	½	67	135	....	Farmer	Factory.	Miss.	Miss.	P	2	Fair.	100	66	3.5	24	4	2	0.5	0	.....	
56	25	1	70	149	....	Stock Farm	Same	Miss.	Miss.	N	....	Xlnt.	100	58	2	32	6	2	0	0	.....	
57	19	1	65	143	149	Canning	Canning	Tex.	La.	N	....	Good.	90	60	7	24	4	5	0	Few	0	Never lived on farm.
58	23	1	70	138	142	Fireman	Farmer.	La.	Miss.	P	2	Good.	90	66.5	2.5	25.5	2.5	3	0	Few	55	
59	28	1	65	123	....	Roxmill	Painter	La.	La.	N	....	Fair.	90	36.5	0.5	49	5.5	8.5	0	0	.....	Never lived in country.
60	25	1	70	135	135	Sawmill	Farmer.	Miss.	Miss.	P	18	Good.	90	30	6	32	15	17	0	Few	13	
61	19	1	69	134	....	Section man	Section man	Miss.	Miss.	P	6	Good.	100	47	1.5	37	5.5	8.5	0.5	0	.....	
62	31	1	65	115	116	Lumbering	Farmer.	Miss.	Miss.	P	18	Good.	100	63	8	24	3	2	0	Many	31	
63	23	1	69	136	139	Pile driving	Farmer.	Fla.	La.	N	....	Good.	90	65	5	24.5	1.5	4	0	Few	11	
64	30	1	70	160	....	Photographer.	Farmer.	Tenn	Tex.	N	....	Good.	100	55	1	29	8	7	0	0	.....	
65	29	1¼	65	138	139	Machinist	Farmer.	Fla.	Fla.	P	4	Pale	90	41	5	48	2	4	0	Few	32	
66	22	1	69	132	132	Express	Express.	Tex.	Tex.	N	....	Fair.	90	54	6	32.5	3	3	1.5	Very few	1	Never lived in country.
67	19	1	67	139	....	Engineer	Clerk	Ga.	Ala.	P	12	Fair.	90	58	2	33	4	3	0	0	.....	Never lived in country.
68	23	1	66	146	140	Clerk	Farmer.	Ala.	Ala.	N	....	Good.	90	55	5	26	5	7	2	Few	18	
69	23	½	69	130	127	Farmer.	Farmer.	La.	La.	N	....	Good.	90	59	13	23	2	2	1	Few	10	
70	22	1¼	70	151	148	Logging	Farmer.	Miss.	Miss.	P	3	Good.	90	49	11.5	28	6	5	0.5	Few	1	
71	23	½	65	142	....	Log scaler	Log scaler	Miss.	Miss.	P	6	Fair.	80	59	2.5	30	3	5	0.5	0	.....	

72	26	¾	70	164	176	Laborer	Farmer	Ga.	Ga.	N	....	Good.	100	62	5	23	5.5	4.5	0	Very few	13				
73	21	½	68	151	146	Coal miner	Lived on farm	Ala.	Ala.	N	....	Good.	100	52	8	37	3	0	0	Many	27				
74	24	½	68	189	....	Salesman	Clerk	La.	La.	N	....	Good.	100	59	0	31	4	5	1	0	.....	Never lived in country.			
75	19	1	67	132	136	Laborer	Laborer	Miss.	Miss	P	5	Pale	100	83	6	9	1	1	0	Very many	77	Laborer in city. Never lived in country.			
76	24	1	67	153	....	Carpenter	Farmer	Miss.	Miss.	N	....	Fair	90	51	6	32.5	4	6	0.5	0	.....				
77	28	2	67	138	....	Bricklayer	Express	La.	Ala.	N	....	Xlnt	100	53	7	26	5	6	3	0	.....	Never lived in country.			
78	21	1½	70	160	164	Cotton mill	Farmer	Ala.	Fla.	P	7	Fair	100	62	4	26	6	2	0	Few	75				
79	22	¾	69	137	138	Fireman	Scholar	Miss.	Miss.	P	12	Good.	100	53	4.5	33	4.5	5	0	Very many	99				
80	25	1½	65	124	....	Waiter	Clerk	Ga.	Ga.	N	....	Pale	90	57	2	20	12	8	1	0	.....	Never lived in country.—Syphilitic.			
81	25	2	6	159	144	Lumberi g	Farmer	Ala.	Ala.	P	15	Good.	100	54	1	27.5	10	7.5	0	Very few	1				
82	23	2	68	165	165	Lumbering	Farmer	Ala.	Ala.	P	11	Good	90	48	11	31	4.5	3.5	2	Very few	3				
83	23	2	68	132	137	Electrician	Electrician	Ala.	Ala.	N	....	Fair	90	24.5	13.5	51	5	5	1	Very many	38				
84	33	2	72	184	....	Lumberman	Farmer	Miss.	Mo.	N	....	Fair	100	49.5	0.5	39	5	6	0	0	.....	Lived in Mo. last 13 years.			
85	33	1	67	150	....	Farmer	Farmer	Tenn	Tex.	N	....	Good.	90	48.5	5	34	5.5	6.5	0.5	0	.....				
86	23	1¼	64	123	117	Laborer	Laborer	Miss.	Miss.	N	....	Fair	80	45.5	3.5	35	10.5	5.5	0	Very few	5				
87	28	2¼	74	175	173	Farmer	Farmer	Miss.	Miss.	P	10	Good.	100	35.5	7	42.5	9	5	1	Very few	15				
88	29	1½	66	139	....	Electrician	Merchant	La.	La.	N	....	Good.	90	65.5	0.5	16.5	9	8	0.5	0	.....	Never lived in country.			
89	26	1	67	142	....	Telegrapher	Clerk	Tex.	Tex.	N	....	Good.	100	68	6	21	3	1	1	0	.....				
90	22	2¼	69	161	....	Telegrapher	Telegrapher	Tenn	La.	N	....	Pale	90	61.5	1.5	21	6.5	9	0.5	0	.....				
91	24	2	67	138	....	Carpenter	Carpenter	Miss.	Miss.	N	....	Pale	90	64.5	4.5	26	2.5	2.5	0	0	.....	Lived on farm till 16 years old. Never farmed.			
92	23	1½	72	164	....	Drummer	Fireman	La.	La.	N	....	Fair	90	54	4	37.5	3	1	0.5	0	.....	Never lived in country since 8 years old.			
93	24	1½	68	137	139	Millman	Farmer	Miss.	Miss.	P	10	Good.	100	38	12	47	1	1	1	Very many	24				
94	31	1	72	184	....	Farmer	Farmer	Miss.	Miss.	N	....	Xlnt	100	45	3.5	36.5	11	3.5	1.5	0	.....				
95	27	2	69	149	....	Clerk	Clerk	Ala.	Tenn	N	....	Good.	90	74	0	23	1	1	1	0	.....	Never lived in country.			
96	23	¾	65	138	136	Brakeman	Millhand	N. C.	S. C	P	15	Good.	100	62.5	3	24.5	4	6	0	Few	10				
97	22	1¼	66	140	136	Circusman	Farmer	Tex.	La.	N	....	Pale	80	56	12.5	28	1.5	1	1	Few	0				
98	32	¾	69	145	....	Machinist	Ironworker	Va.	Va.	N	....	Fair	90	61.5	5	27.5	2.5	3.5	0	0	.....	Few ova tricocephalus dispar.			
99	23	1¼	65	136	....	Salesman	Salesman	Ky.	La.	N	....	Good.	100	57	2	35.5	3.5	2	0	0	.....	Never lived in country.			
100	24	1½	70	144	....	Smith	Painter	Va.	Ala.	N	....	Good.	100	56	3	30.5	5.5	5	0	0	.....	Never lived in country.			

Thirty-one cases of uncinariasis out of 57 = 54 per cent.
Average eosinophilia for positive cases, 6.85 per cent.
Average eosinophilia for negative cases, 2.50 per cent.
Average weight of positive cases, 141 lbs.
Average weight of negative cases, 148 lbs.
Average gain in weight after treatment, 0 lbs.

* N means negative history for ground-itch.
P. means positive for ground-itch.
Xlnt. means "Excellent."

cent. infected. My own work in this direction was brought to an unexpected conclusion because of the sudden cessation of recruiting in New Orleans made necessary by reason of the fact that the army had nearly reached its authorized strength.

Strong reports[2] that in an investigation of 4,106 Filipino prisoners 52 per cent. were found to be infected with uncinaria. If this can be taken as an index for the general population of the Philippines, it appears that the proportion of infections among the Filipinos, living in their insanitary manner, is not as high as that of southern-bred recruits who probably are less likely to be infected than the mass of the rural population of the south.

CLINICAL SIGNS OF LIGHT INFECTIONS

First of all, it must be clearly understood that none of these infected subjects studied by me were sick. Many never had been on sick report, and, of those who had, only one presented symptoms which, in the light of positive uncinaria findings, could be attributed to the parasites. This patient had been in hospital several times with slight fever, indefinite intestinal symptoms and fleeting pains in chest and abdomen. He was unable to do any heavy work without soon becoming used up. Hemoglobin was 80 per cent. Seventy-seven worms were obtained after he was treated. With this exception, the cases I am reporting belong to the class of which Stiles says: "Under light infections may be included those patients who show eggs in the feces on microscopic examination, but who do not exhibit any or sufficiently marked symptoms to attract special attention. These cases are numerous and important, as they are capable of keeping a region infected and thus giving rise to severe cases. Hence from a prophylactic standpoint they should always be treated when found." That these cases can not be detected by mere inspection is evidenced by the words of Stiles, that "if these light cases were submitted to physical examination for enlistment in the army or navy, probably most of them would be accepted as sound."

As will be seen in the appended tables, I have classed the color of the men examined as "excellent," "good," "fair" or "pale." By "excellent" is meant the fresh, ruddy complexion so common among healthy northern men. It will be observed that very few of the southern men possessed this "excellent" color. Many are recorded as fair and a few as pale, but there

2. Strong (R. P.): Combating tropical diseases in the Philippines by scientific methods. Jour. Am. Med. Assn., 1909, lii, 524.

seem to have been no notable differences in color between the positive and the negative cases.

In view of the great prevalence of uncinariasis in the South, it is thought that much caution must be used in looking on hookworms as the cause of atypical symptoms in a patient simply because the ova are found in the feces, since the presence of uncinaria in the intestines may be a mere coincidence.

TABLE III.—FOUR CASES OF UNCINARIASIS FOUND AMONG THIRTY-THREE UNSELECTED SOUTHERN-BRED SOLDIERS WHO HAVE SERVED MORE THAN ONE ENLISTMENT PERIOD (OVER THREE YEARS)*

Case No.	Age.	Years in Army.	Height, inches.	Weight before treatment.	Weight after treatment.	Occupation at time of enlistment.	Occupation previous to enlistment.	Birthplace.	Residence.	History of ground itch.	Color.	% hemoglobin.	% polynuclears.	% eosinophiles.	% lymphocytes, small.	% lymphocytes, large.	% transitionals.	% mast cells.	Number of ova found in stool.	Number of worms found after treatment.
109	26	4	68	156	148	Farmer....	Logging...	Tenn...	Tenn...	N	Good	90	55	4	31	5	4	1	Very few	2
127	22	5	71	140	140	Machinist.	Farmer ...	N. C...	N. C....	N	Fair.	90	50	8	38	2	2	0	Many	11
129	29	6½	68	145	140	Salesman.	Farmer....	Miss...	Miss...	N	Good	90	55.5	10.5	24	4.5	5	0.5	Very few	6
132	28	7	65	156	160	Farmer....	Farmer....	Tenn...	Tenn...	N	Fair.	90	31.5	26.5	36.5	3	2.5	0	Very few	3

* Twenty-nine negative cases are omitted from table as showing nothing of interest.
N. means negative for ground-itch.
Average eosinophilia 4 positive cases, 12.5.
Average weight 4 positive cases 149.7 lbs.
Average number of worms found, 5½.

BLOOD APPEARANCES IN MILD INFECTIONS

The reduction in hemoglobin in infected men was very slight, being less marked than was found in the cases reported by Siler. No case was found with the hemoglobin lower than 80 per cent; the majority showed 90 per cent. and a considerable number 100 per cent. Among the 133 southern-bred men the average hemoglobin percentage for the infected cases was 91.5 per cent. and for the non-infected 94.2 per cent., a difference of only 2.7 per cent. No counts of red cells were made.

The leucocyte count was made in 12 infected cases, but, as it did not seem to show anything of interest, it was discontinued. The highest count was 12,700, the lowest 7,600, and the average 9,600 per cubic millimeter.

A differential count of the white cells was made in all cases and demonstrated, as was to be expected, that eosinophilia was present in the majority of those harboring hookworms. In the 64 positive cases the lowest eosinophile count was 1 per cent. and the highest 26 per cent. Fourteen cases showed less than 5 per cent. of eosinophiles. The average eosinophile count for the 64 infected cases was 8.5 per cent., and for 83

non-infected cases 2.2 per cent. In the 83 negative cases, only 9 subjects showed an eosinophile count over 5 per cent., and, of these, 2 were infected with *Trichocephalus dispar,* which doubtless caused the eosinophilia. From these observations it appears that an eosinophilia of over 5 per cent. is a very strong point in favor of infection with an intestinal parasite, but that one below 5 per cent. is of no value in excluding infection with *Necator americanus.*

THE PARASITES

Of the 64 patients in whom ova of uncinaria were demonstrated in the feces, 4 left before treatment. The remaining 60 patients were treated in the usual manner with 4 gm. of thymol, and worms were recovered from the stools of 56. The smallest number found was 1, the largest 99, and the average number per patient was 16. Whether this represents the entire amount of infection is not yet known, as very few of the patients have been re-examined since treatment, and it is probable that some worms still remain in many of the patients. The majority of the men interrogated some weeks after treatment reported that they felt better than before; one did not feel so well, and a few noted no change, these last being patients from whom only 2 or 3 worms were obtained.

All of the parasites are believed to have been American hookworms. Specimens from half of the cases were sent to Dr. C. W. Stiles for identification, and he reports that all were *Necator americanus.*

In the examination of the entire 147 men, it was surprising to find the ova of other parasites in only 3 cases, all of the 3 being infections with *Trichocephalus dispar.*

LONGEVITY OF THE HOOKWORM IN THE INTESTINES

The length of time the parasite will live in the intestines seems to be in doubt, but that it may sometimes be a period of several years appears probable from my findings. The habits of the soldier and the sanitary conditions at this and practically all other army posts are such that reinfection with uncinaria larvæ is not probable. In the new recruits examined, 67 per cent. of infection was found; in the soldiers in their first enlistment, 54 per cent., and in those in subsequent enlistments, 11 per cent. This apparently indicates that there is a tendency for the worms in the soldier's intestine to die out gradually. This tendency, however, is not always rapid, as is shown by the persistence of the infection in some cases even to the fourth, sixth and seventh years of service.

DIAGNOSIS

In the cases like those covered by this report the general appearances and ordinary physical examination are of no diagnostic value. Diagnosis must rest solely on the microscopic findings. As stated above, an eosinophilia of over 5 per cent. is very suggestive, but one below that by no means excludes uncinariasis. In these light infections the finding of ova in the feces is often a tedious process. I made my examinations by mixing a bit of feces with water and covering with a seven-eighth-inch coverglass. In Tables 1, 2 and 3 I have recorded the number of eggs in the stools as "very few," "few," "many" and "very many." If two or more slides were gone over before a single egg was found, the record "very few" was made. If one or two ova were found in a slide, the record was "few." The tables show "very few" in 18, or 28 per cent., of the 64 cases, which means that at least two slides were gone over before an ovum was found. In several cases six or eight slides were examined before the first egg was discovered.

In some cases the number of eggs found in the feces seemed to bear no relation to the number of worms passed after the first course of treatment.

SOURCE OF INFECTION

In this series of cases, the findings coincide with previous experience as to the importance of rural life as a predisposing cause of infection. Among the 64 infected subjects, 53 gave a history of having at some time worked on a southern farm. Of the 11 remaining subjects 3 were laborers, 2 firemen and 1, each, a plumber, country blacksmith, expressman, brakeman, electrician and canning factory employé. Only 4 infected subjects reported never having lived in the country, and, of these, 1 was a laborer, 1 an expressman, 1 a locomotive engineer and 1 worked in a factory canning shrimps and oysters.

Among the 100 recruits and soldiers in their first enlistment, 74 had been farmers at some period of their lives, the percentage of uncinariasis among these being 81 per cent. This closely approximates the findings of some physicians who have asserted that in parts of the south 90 per cent. of the rural population is affected with hookworm disease.

Most of the men gave a history of having gone barefooted in childhood, and a little over half reported having had ground itch, but in most cases the last attack was stated to have been a great many years before, so it is doubtful if much importance can be attached to that feature in this series (Tables 1, 2 and 3).

RELATION OF UNCINARIASIS TO THE PHYSICAL DEVELOPMENT OF RECRUITS

It is considered by many recruiting officers that the physical development of the southern applicants for enlistment is below that of northern men, and it is known that a great number of southern men are rejected at the recruiting stations for poor physical development and weight under that required. The observations made by myself, as well as by other army surgeons, have given the impression that the southern recruits are poorly developed and poorly nourished. Some statistics from the records of the examination of recruits at Jackson Barracks confirm these impressions, as indicated by Table 4.

TABLE IV—HEIGHT AND WEIGHT OF RECRUITS

	Average Height.	Average Weight.	Relation of Weight to the Army Standard
149 recruits not born in south	66	145	13 lbs. above.
308 recruits born in the south	68 2/5	141⅔	2 1/3 lbs. below.
70 southern-born farmer recruits	68 1/6	140	2 1/6 lbs below.
64 soldiers with uncinariasis	68 3/7	140½	3½ lbs. below.

Siler considers it probable that the poor development of the southern recruit is due to uncinariasis. In this connection these words of Stiles are of interest: "If infection occurs before puberty, it is likely to retard development, both mental and physical." My own work shows that the average weight of the infected cases was lower than that of the non-infected southern soldiers, though the difference is not very marked among the new recruits.

TABLE V—WEIGHT OF INFECTED AND NON-INFECTED SOUTHERN RECRUITS

	Average Weight.	Difference.
14 southern recruits not infected	143	
29 southern recruits infected	140¼	2¾ lbs.
26 southern soldiers in first enlistment non-infected	148½	
30 southern soldiers in first enlistment infected	142	6½ lbs.

As seen in Table 4, the average weight of 64 infected soldiers, as compared with their height, was 3⅝ pounds below the army standard, while the average for 149 northern-born recruits was 13 pounds above.

Whether the eradication of the parasites at the age of the average soldier will lead to an increase in weight is left in uncertainty by my observations. Siler reports a constant gain in weight in recruits after treatment. My 29 recruit patients, weighed about five weeks after treatment, showed an average gain of 3½ pounds. It is not fair, however, to attribute a gain of weight in recruits solely to the fact that they have been relieved of their hookworms, because it has been found that under ordinary circumstances recruits gain weight as a result of the regular life, good food, excellent sanitary conditions and graduated exercises associated with the military life.

Among 34 seasoned soldiers, weighed on the average about one month after treatment, there was a total loss of 11 pounds, or about one-third of a pound per man. Some men gained markedly, while others lost as heavily. It is thought that further treatment of such as may be found still to harbor worms may show, if the patients be weighed one or two months later, after the effects of treatment have fully passed off, that eradication of the worms has favorably affected the weight.

PROPHYLAXIS

It is probable that any applicant for enlistment in the army who has a marked infection with uncinaria will be detected by the ordinary examination given a recruit. The light infections which escape the examining officer apparently do not affect materially the efficiency of the soldier and do not, in the patients' interest, urgently demand treatment. From the standpoint of prophylaxis, however, thorough treatment of the mild infections is of great importance both in the army and in civil life. It is probable that there are hundreds, perhaps thousands, of cases of mild uncinariasis in the army, some of which may be setting up new foci of infection in localities hitherto free from the disease. Just as the typhoid bacillus-carrier is a menace to the community, so is the hookworm-carrier, and the treatment of the comparatively few carriers in the military service and the countless ones outside the army will be one of the steps absolutely necessary if the disease in its severer manifestations is to be eradicated from the south.

CONCLUSIONS

1. Infection with uncinaria is very common among southern-bred soldiers during the first three years of service. In 100 men examined, 60 per cent. showed uncinariasis. Among new recruits the percentage of infections is at times as high as 85.

2. Southern-bred soldiers with more than three years' service show a much lower percentage of infection, only 11 per cent. in 33 cases.

3. The worms gradually die out, most of them during the first three years, and under the favorable sanitary conditions obtaining in the army at home reinfection occurs rarely, if at all.

4. The symptoms produced by a light infection with hookworms are so slight that they can not be detected by the usual methods employed by the examining surgeon, and diagnosis must be made with the microscope.

5. An eosinophile count of over 5 per cent. is very strong evidence of infection with an intestinal parasite, but one below 5 per cent. is no evidence against uncinariasis.

6. The parasite in probably all cases is *Necator americanus*.

7. In some cases the worm probably lives several years in the intestines.

8. In many light infections, the ova are difficult to find, requiring the complete examination of five or six cover-glass preparations.

9. Farm life is very important as a predisposing cause. Among 74 men who had farmed at some time, 81 per cent. were infected.

10. Most of the men had gone barefooted in childhood, and over half reported having had ground itch, though usually not since childhood.

11. Southern recruits are less well developed physically than northern ones.

12. Uncinariasis in childhood is a very probable cause of this underdevelopment.

13. Light infections do not materially affect the efficiency of the soldier, though the majority report that they feel more vigorous after treatment.

14. Treatment of the light infections is of great importance in any attempt to stamp out the disease.

DISSEMINATED MILIARY TUBERCULOSIS OF THE SKIN

AN IMPORTANT SIGN IN GENERAL MILIARY TUBERCULOSIS OF INFANCY *

WILDER TILESTON, M.D.
BOSTON

The purpose of this article is to call attention to the occurrence in infantile miliary tuberculosis of a skin eruption, which, although occasionally described in the past, is rarely alluded to in the current text-books of medicine and pediatrics, and is apparently seldom recognized by the profession. And yet this rash is fairly common in the tuberculosis of infancy, and at that age is almost pathognomonic of general miliary tuberculosis. It consists of scattered discrete papules, which at the beginning are the size of pin-heads, and are soon capped by tiny vesicles with cloudy or purulent contents. Later on, the vesicle ruptures or dries up, and its place is taken by a crust. It is this stage which is most characteristic. The lesion is now 2 to 3 millimeters in diameter; that is to say, about the size of a rose spot in typhoid fever, and consists of a flat papule, only slightly elevated, of a dull red color, often glistening. The center is occupied by a crust, on the removal of which there is disclosed a minute but sharply defined dell or hollow, varying in size from the point to the head of a pin. Healing takes place in case the child lives long enough, leaving a tiny white scar surrounded by a halo of brownish pigmentation. I have been unable to determine the exact duration of the individual lesion, but it probably varies from one to several weeks. The spots appear in crops, so that all the different stages may be present at the same time.

Rarely a vesicular type of eruption is seen, with vesicles up to the size of a small pea, surrounded by a slightly elevated area of redness and infiltration. This form likewise shows, when in the crusting stage, the characteristic hollow in the center.

The distribution is fairly constant, the majority of the spots being situated on the buttocks, genitalia and adjacent portions of the thighs; i. e., on the parts covered by the diaper. This is probably due to irritation by the feces and urine, with consequent lowered resistance of the skin. The abdomen, front of the chest, thighs and legs, and sometimes the arms, face, neck, palms and soles may show a few spots; the back is usually free, except the buttocks. The eruption is not, as a rule, sym-

*Delivered before the Boston Society of Medical Sciences, April 27, 1909.

metrical and is seldom profuse, the total number of spots usually not exceeding twenty to thirty, while often only half a dozen are present. They never become confluent.

Once seen, this rash is readily recognized, and, if the characteristic umbilication is present, is not likely to be confused with any skin disease with which I am familiar. The vesicular type may be distinguished from varicella by means of the central crater. Molluscum contagiosum is umbilicated, but the lesions are more globular, are transparent, constricted at the base, and on pressure yield a creamy fluid containing the peculiar molluscum "corpuscles." Syphilitic eruptions in infants do not show umbilication, nor does acne.

FREQUENCY

Out of thirty-two cases of tuberculosis in children in the first three years of life, examined by me, seven, or 21 per cent., have shown the eruption. In view of the fact that most of the children were seen only once or twice, the real proportion must be considerably higher. The list includes cases of tuberculosis of the bones, lymph nodes, lungs, intestines, meninges and peritoneum. All the children with spots who came to autopsy were found to have miliary tuberculosis. It is by no means unlikely, however, that a few spots may appear on the skin in cases with localized tuberculosis, as occurs in older children and adults. In general, the more chronic cases are more apt to show spots, while in the acute ones the patients probably die before the eruption has time to develop. Thus out of fourteen patients with tuberculous meningitis, only one had spots. Two hundred children suffering from various diseases, other than tuberculosis, all failed to show any eruption resembling the one under consideration.

It is evident that the exanthem described above is of little significance of itself, for it causes no symptoms and shows a rather marked tendency to heal. From the point of view of diagnosis and prognosis, however, it is of the greatest importance, for all of the ten patients who form the basis of this report have been the subjects of general miliary tuberculosis, and all have died.

HISTOLOGY

In spite of the very constant gross appearances, there is a wide range of variation in the histologic picture. The most acute type shows simply necrosis of the skin and adjacent subcutaneous tissue, entirely without inflammatory reaction of the surrounding area; there is no round-cell infiltration, no giant or epithelioid cells. In other cases, there is a chronic

inflammatory tissue with epithelioid, lymphoid and plasma cells, but no giant cells or tubercles. Here there is nothing to suggest tuberculosis except the presence of tubercle bacilli. And, lastly, there may be a typical tuberculous process, with caseation and the formation of miliary tubercles and giant cells.

ETIOLOGY AND PATHOGENESIS

The cause of the eruption is the tubercle bacillus. In 70 per cent. of my cases, tubercle bacilli were demonstrated within the skin lesions, sometimes in large numbers. In others, to be sure, the bacilli were so scanty that they were found only after a prolonged search. The 30 per cent. of negative findings is not surprising in a chronic lesion showing little tendency to spread; it may be accounted for either on the supposition that the bacilli have died out, or that they were not brought out by the staining methods employed. The occasional failure of tubercle bacilli to take the carbol-fuchsin stain in sections is well recognized.

The association with miliary tuberculosis and the presence of tubercle bacilli in the capillaries (in Case 1) leave little doubt as to the mode of origin of the process; it is embolic, analogous to the formation of rose spots in typhoid and to the pustular efflorescence of staphylococcus septicemia.

The following cases, seven of which came under my observation during life, will serve to illustrate the character of the rash and show its value as a diagnostic sign of miliary tuberculosis:

CASE 1.—*Patient.*—J. P., a male infant, born at Long Island Hospital, Boston, Oct. 29, 1907; weight at birth, 9 pounds; at two weeks, 8 pounds 5 ounces. Discharged Nov. 18, 1907, in good condition. Readmitted May 18, 1908, aged 7 months. No history obtained. Temperature, 100.2; pulse, 120; respiration, 41.

Physical Examination.—A fairly developed, rather poorly nourished male baby, pale and fretful; a few small lymph nodes palpable in neck, axillæ and groins. Head square; marked rosary. Lungs: A little outside the inferior angle of the scapula on the right, consonating râles and bronchial breathing, without dulness; elsewhere scattered moist râles. Liver palpable 5 cm., spleen 3 cm., below the costal margin. Over the chest, back, abdomen and thighs, about thirty small reddish spots about 3 mm. in diameter, slightly elevated, many covered with crusts, some showing distinct depressions in the center.

Course of Disease.—Being at the time unfamiliar with the eruption, I made the diagnosis of congenital syphilis, with bronchopneumonia. On the 19th the temperature rose to 104. The baby died on the following day.

Autopsy (Dr. T. Ordway).—This showed a very extensive general miliary tuberculosis, involving the heart, lungs, peritoneum, liver, spleen, pancreas, kidneys, aorta and skin. The meninges, however, showed only one or two tubercles. There was also tuberculous bronchopneumonia with caseation and cavity formation, tuberculous adenitis and tuberculous ulcers of the intestine. The starting place of the general infection was apparently a cavity in the right lower lobe. Sections of the skin lesions showed focal necrosis, surmounted by the remains of

vesicles; the necrosis was most marked at the epidermis, but involved all the layers of the skin and even the subjacent subcutaneous tissue. There was no caseation, no tubercle formation, in fact, no cellular reaction. Tubercle bacilli were found in large numbers, in the necrotic subcutaneous tissue and also on the free surface. Occasionally bacilli were present in well preserved capillaries in the necrotic area. The tubercles in the various viscera were also characterized by foci of necrosis with little reaction on the part of the surrounding tissue and absence of giant cells.

CASE 2.—*Patient.*—C. S., a female negro child, aged 1 year 9 months, was seen by me May 23, 1908. She had been well up to three weeks previously, when she began to have a short hacking cough and to vomit. The vomiting lasted four days, the cough continued. Convulsions daily for the past six days.

Physical Examination.—Fairly developed, moderately emaciated. Temperature 102. Large rachitic rosary, epiphyses enlarged, legs bowed. Head somewhat retracted, stiff. Pupils dilated, reacting sluggishly to light. Legs extended, crossed and very rigid, back also stiff, arms less so. Dyspnea. Hyperresonance of chest, with decrease of cardiac dulness; liver dulness at seventh rib. The lower half of the chest showed numerous fine moist crackles. Spleen palpable 2 cm., liver 3 cm., below costal margin.

Skin: Close inspection showed five papules, three on the front of the chest, one on the epigastrium and one on the right thigh. They varied in size from a pinhead to 2 mm. in diameter, were dull red, slightly elevated and covered with a tough brown crust, which was closely adherent. On removal of the crust there was seen a small hollow in the center of the papule, which bled slightly.

Course of Disease.—The finding of these spots, which resembled those in the first case, led me to make the diagnosis of tuberculous meningitis with general miliary tuberculosis. The following day a fine purpuric rash appeared on the abdomen. By lumbar puncture 5 c.c. of slightly turbid fluid was obtained; it clotted on standing and showed 78 per cent. mononuclear, 22 per cent. polynuclear leucocytes; tubercle bacilli not looked for. Death took place the same day, May 24.

Postmortem Examination.—No autopsy was obtained, but the spots were excised postmortem, and a few tubercle bacilli were found in them. Histologically they showed a chronic inflammatory process, with central necrosis corresponding to the hollow observed during life. There was infiltration with lymphoid, epithelioid, and plasma cells, but no tubercle formation.

CASE 3.—*Patient.*—H., a male infant, 3 months old, entered hospital June 20, 1908. The parents were Irish; the father had tuberculosis of the lungs. The baby was one of twins, and was breast-fed three weeks; well up to two weeks before entrance, when he took cold. Bowels moved six times a day; stools green. Appetite good. Nose-bleed two days before entrance. Temperature 39.8, weight 4,730 gm.

Physical Examination.—Fairly developed and nourished, no rosary. A small hydrocele on each side. A few râles at the right base behind. Abdomen much distended, superficial veins prominent. Both the liver and spleen enlarged and palpable, the former reaching 6 cm. below the costal margin, the latter to the umbilicus. The abdomen was somewhat tender generally, and there was a small amount of shifting dulness. Clinical diagnosis: Tuberculous peritonitis. Hemoglobin 80 per cent; white count, 10,000. Urine pale, clear, acid, no albumin or sugar. On June 25 I saw the patient and observed a characteristic eruption. It consisted of 40 discrete papules, 1 to 3 mm. in diameter, each with a well marked central crater. They were most numerous on the buttocks, thighs and scrotum, with a few on the legs, feet and chest, none on the head. Some were dark red, others were evidently involuting, being paler, barely elevated above the surround-

ing skin, and covered with a thin scale. On the back of the right little finger was a pustule with injected periphery, covered with a brown crust, the removal of which revealed a broad, shallow, red glistening depression.

Histologic Examination.—On June 26 two of the lesions were excised, and showed on histologic examination an infiltration with lymphoid, epithelioid and plasma cells, with central necrosis corresponding to the umbilication; no giant cells, caseation or tubercle formation. Tubercle bacilli found in small numbers.

Later History.—The ocular tuberculin reaction was doubtful with 0.5 per cent. solution; positive with 1 per cent. During the nine days' stay in the hospital the baby lost 430 grams in weight, there was irregular pyrexia, ranging from 36.6 to 30.2 C.; pulse 120 to 180, respiration 40 to 95. Two to six dejections daily, green or brown with mucus and curds, but no blood. The patient was discharged June 29, and died at home July 4, 1908. No autopsy.

CASE 4.—*Patient.*—A., a male Italian child, 3 years old, entered the hospital June 20, 1908, for fever and cough of seven weeks' duration, accompanied by loss of weight and weakness. Previous history negative.

Physical Examination.—Fairly developed and nourished child, pale, with a rosary and enlarged epiphyses. The lungs showed numerous scattered moist râles on both sides, without definite signs of consolidation. In the *x*-ray plate, however, were small patches of shadow scattered throughout both lungs. Liver and spleen both enlarged, the former reaching 8 cm. and the latter 6 cm. below the ribs. Red cells, 2,600,000; no leucocytosis. There was an irrgular remittent fever, with a maximum of 103.5. On June 22 I saw the child, and found four typical papules, dull red, flat, slightly elevated, some with an adherent crust, all showing the central hollow, size 2 mm., distribution as follows: One on the right side of the neck, one near the right nipple, one on the right flank and one in the left groin; on the buttocks, two smaller red papules without crusts or umbilication. Two of the papules were excised the next day and showed the usual structure of these lesions, with marked infiltration with epithelioid, lymphoid and plasmic cells, but careful search through serial sections failed to show tubercle bacilli. The skin tuberculin reaction (von Pirquet) was negative.

Later History.—The patient failed gradually and died July 17, 1908. Autopsy refused. The clinical diagnosis was miliary tuberculosis, but exact proof was wanting. The case is included in the present series on account of the typical gross and microscopic appearances of the skin lesions, occurring in a case which closely resembled miliary tuberculosis.

CASE 5.—*Patient.*—C. L., a female child of 2½ years, entered the Boston City Hospital, South Department, September 17, 1908, with laryngeal diphtheria. The parents were Swedes. The mother's father and a great-aunt died of tuberculosis. The child had had summer diarrhea two years previously, and measles. The present illness began four days before entrance with "cold in the head and choking." On admission she wore a laryngeal tube. Antitoxin was administered; temperature normal on third day at hospital. The tube was removed September 20.

Course of Disease.—On the 24th a recurrence of fever and stenosis of the larynx made intubation again necessary, and more antitoxin was given. Spasmodic cough was noted on October 2, sometimes followed by vomiting, and the diagnosis of pertussis was made. Three cases of undoubted pertussis developed in the same ward soon after. The temperature was constantly elevated from September 19 till the death of the child on November 13, ranging usually from 100 to 102 or 103, with morning remissions; the maximum was 104.5. The respiration was increased in rate, varying from 30 to 65. Numerous fine and coarse râles soon appeared scattered over both sides of the chest, and the spleen became palpable 2 cm. below the costal margin. There was a leucocytosis of 28,400 (Oc-

tober 14), with "mononuclears increased." The liver was felt 3 cm. below the edge of the ribs. Urine, no albumin. On October 23 the spleen had increased further in size, the liver reached nearly to the navel, and a skin eruption was noted, consisting of numerous small papules on the abdomen and legs. This rash is said to have been already of two weeks' duration. One of the papules was excised October 29 by Dr. Ordway. He describes it as a typical lesion with central umbilication. The sections showed tubercle bacilli in large numbers, often aggregated in heaps. Blood culture was negative.

Examination.—Several days later I saw the child, and found a copious eruption of about 75 papules, chiefly on the chest, abdomen, buttocks, external genitalia, thighs and arms. The spots were 2 mm. in diameter, red, soft, with a vesicle in the center. On the back were two larger lesions, resembling echthyma, covered with thick yellow crusts. The von Pirquet skin reaction was negative (October 27). Signs of consolidation in the right middle and lower lobes appeared and death occurred November 13. There were no signs of meningitis.

Autopsy (Dr. Ordway).—There was found very extensive general miliary tuberculosis, involving almost all the viscera excepting the brain and meninges. There was also caseous bronchopneumonia and tuberculosis of the bronchial, mediastinal, mesenteric and retroperitoneal lymph nodes. The skin showed still a few papules, reddish-white, firm, some with a central brown crust, others with a minute central depression.

CASE 6.—*Patient.*—A., male infant, Italian, 9 months old at entrance to the hospital, Dec. 11, 1908. The mother was then in the last stages of phthisis. Past history not obtained.

Course of Disease.—The child had been sick four days with cough and fever. There was a patch of solidification near the inferior angle of scapula on the left; the spleen was palpable 2 cm. below the costal margin. Diagnosis: Pneumonia. Resolution took place, but fever continued, an irregular pyrexia with remissions, maximum 40.4, minimum 37.2. On January 4 an area of ill-defined consolidation appeared on the other side, in the lower lobe, and there were diffuse moist râles. On the 18th the tuberculin skin reaction was negative. In spite of this, a diagnosis of tuberculosis of the lungs was made, on account of the clinical course of the disease.

Examination.—I saw the patient for the first time on January 22, and found a very characteristic rash, which the nurse said had been present for a long time. There were about sixty discrete papules, chiefly on the buttocks, thighs and scrotum, 2 to 3 mm. in diameter, flat, only slightly elevated, dull red in color, with a glistening surface, and a pin-point depression in the center. Some of these were evidently in the process of healing, being flush with the surrounding skin, with brown pigmentation, and at the periphery a slight furfuraceous desquamation. There were a few similar papules on the neck. Back and legs free. Over the abdomen, arms and face there were much smaller, pin-point yellowish crusts which on removal left a minute dell in the center. To the left side of the anus was a purple indurated area with a recent incision discharging pus (ischiorectal abscess). On the antihelix of the right ear was a small, rather deep ulceration covered with a crust. Examination of the chest showed below the right clavicle amphoric breathing with dull tympany on percussion. There was consolidation at left base behind, consonating râles without dulness in right mid-back, moist râles everywhere; pallor, lividity and dyspnea. On the strength of this eruption a positive diagnosis of general miliary tuberculosis was made. Later in the day sputum was obtained, and showed numerous tubercle bacilli.

The baby died three days later, January 25.

Autopsy (Dr. C. H. Dunn).—This showed a profuse general miliary tuberculosis, involving the lungs, liver, spleen and kidneys, with tuberculous pneumonia, two small cavities at the right apex, tuberculosis of the intestines. Sections of the papules showed infiltration, chiefly with epithelioid cells, no distinct tubercle formation, no giant cells. Tubercle bacilli were distributed in large numbers throughout the lesion.

CASE 7.—*Patient.*—P., a Portuguese boy, 3 years old, entered the hospital March 3, 1909, for phlyctenular keratitis. Past history could not be obtained. I first saw the patient March 10, 1908, and made the following notes:

Examination.—Well developed and nourished. Scrofulous facies, with broad, thick nose and crusty eczema about anterior nares and ears. Phlyctenular keratitis on left, right eye shrunken from old panophthalmitis. A large bunch of enlarged lymph nodes on each side of the neck, glands in axillæ considerably, in groins slightly, enlarged. Consolidation of left lung from apex down to the fourth rib in front, and to the lower third of the scapula behind; less extensive signs at right apex. Numerous râles throughout chest. Spleen palpable 3 cm., liver 2 cm., below costal margin. Abdomen protruding, tympanitic, no demonstrable ascites. On legs and thighs numerous round pigmented scars 1 cm. in diameter (from impetigo?).

Eruption: About sixty small spots, 2 to 3 mm. in diameter, chiefly on buttocks and thighs, fewer on the legs, one on the left cheek, a few on the neck, none on the chest. Only two of these lesions are fairly fresh, being elevated, dull red, with a good-sized central hollow. The others are in various stages of involution; many are no longer elevated, but consist of whitish scars with a pigmented periphery; a minute central depression in still visible, however.

The two freshest lesions were excised. The sections differed from those of most of the other cases in showing typical miliary tubercles with giant cells. In spite of this, however, and of the typical naked eye appearances, no tubercle bacilli could be demonstrated.

Course of Disease.—The cutaneous reaction of von Pirquet, performed on March 13, was markedly positive, showing a raised red infiltration, 7 mm. in diameter. The sputum showed scanty tubercle bacilli, eight bacilli in four preparations on March 15, five bacilli on March 16. On March 21 all the spots had faded, showing minute whitish scars in the center of a small pigmented brown area. The child was discharged April 4, and died at home April 13, 1909.

These seven cases all came under my personal observation, and tubercle bacilli were demonstrated in the skin lesions in five of them; i. e., in 71 per cent. Either Dr. F. B. Mallory or Dr. S. B. Wolbach confirmed the identity of the bacilli in every instance.

Through the courtesy of Dr. S. B. Wolbach and Dr. T. Ordway, I have been able to examine sections from three other cases, in which the spots were found only at the autopsy. All were cases of general miliary tuberculosis.

CASE 8.—*Autopsy* O-1331, Bender Hygienic Laboratory, Albany, by Dr. S. B. Wolbach. L., an emaciated white male infant, 3 months old. On the right side of the abdomen and on the ankle were two slightly raised, crusted lesions, 1 mm. in diameter. On picking the crust off from one, a crater-like depression was left, which was clean and dry. On the right thigh was a slightly raised, irregular red area, 3 mm. in diameter. There was general miliary tuberculosis, involving the lungs, liver, spleen and kidneys. The primary focus was apparently

in the lungs, which showed extensive caseous tuberculous pneumonia. There was also tuberculosis of the pleura and of the mesenteric lymph nodes. The spots showed the usual histologic appearances, with a few tubercle bacilli. In this case, in which the clinical diagnosis was uncertain, Dr. Wolbach was able to make a positive diagnosis of miliary tuberculosis from the skin eruption, before opening the body.

CASE 9.—*Autopsy* O-1381, Bender Hygienic Laboratory, Albany, performed by Dr. Wolbach, January 30, 1909.—S., a well-developed, fairly well-nourished white female infant, aged 4 months. Eruption: Uniformly distributed over the chest and abdomen there were twenty-three minute papules. The greater number were dry, crusted elevations, 0.5 to 1 mm. in diameter. The removal of the crusts of some of these left clean depressions, some of which were dry and apparently covered with epidermis. Some of the papules were glistening and reddish, others covered by a superficial layer of epidermis, and when incised yielded minute droplets of puriform material. There were a few small papules of both types on both thighs and legs, and several on the neck and right upper arm. There was general miliary tuberculosis of the lungs, liver, spleen, kidneys and aorta. The head was not opened; spinal meninges and cord normal. The right lung showed caseous tuberculous pneumonia of the middle lobe and of the adjoining portions of the upper and lower lobes. There was tuberculous adenitis of the bronchial, mediastinal and mesenteric lymph nodes; tuberculous ulcers of the intestine.

In this instance also the diagnosis, previously in doubt, was made by Dr. Wolbach from the skin eruption. The examination of the spots, however, failed to reveal tubercle bacilli, even after persistent search. This may be due to the fact that only the pus-bearing vesicles were excised; the more typical umbilicated lesions were not examined. The typical gross appearance of some of the lesions and the presence of tubercle bacilli in vesicular lesions in Case 1 leaves little doubt that this case belongs in the present series of tuberculous skin eruptions.

CASE 10.—*Patient.*—T. R., a white female child, 4 months old, entered the Boston City Hospital March 12, 1909, on the service of Dr. C. F. Withington, to whom I am indebted for the clinical notes. The mother had pulmonary tuberculosis. One brother died in infancy of malnutrition, one sister died of bronchopneumonia. The past history was negative; the child was bottle-fed. The present illness began one week previous to admission, with vomiting; three days later there were convulsions, restlessness and violent spells of crying.

Examination.—A well-developed and well-nourished, apathetic child; pupils equal, reacting to light. Neck slightly retracted. Lungs and abdomen negative. Knee-jerks normal. Leucocyte count 20,000.

On the following day there were frequent convulsions, the lungs were full of râles, and the child died after an illness of only nine days. Clinical diagnosis, tuberculous meningitis.

Autopsy, A 09-36, March 14, 1909 (Dr. T. Ordway).—Eruption: On both thighs and buttocks, and to a less extent on the legs, were a few scattered dark red areas, 1 to 3 mm. in diameter, some macular, others papular; the majority had a distinct depression in the center, and were capped by a grey-white scale or crust; individual lesions of similar appearance were found as follows: Right side of neck, right hand, lower abdomen, sole of right foot (some of these resembled fading lesions of varicella). There was general miliary tuberculosis of the lungs, pleura, spleen, liver, kidneys, with tuberculous meningitis, tuberculous bronchopneumonia and tuberculous adenitis of the bronchial, mediastinal and mesenteric lymph nodes. Sections of the skin lesions showed chronic inflammatory tissue with a few tubercle bacilli.

The following case illustrates a rare type of embolic lesion in miliary tuberculosis, that of the subcutaneous nodule:

CASE 11.—*Patient.*—D., a female infant, 15 months old, entered the hospital April 26, 1909, and was seen by me the following day. The mother had died of phthisis one month previously. The baby was bottle-fed; had been constipated since birth. Three months ago a physician made the diagnosis of tuberculosis of the lungs and of a finger. About nine days before admission the child began to vomit frequently; for two days it had been more or less unconscious, with frequent twitchings.

Physical Examination.—Well-developed, rather poorly nourished baby; comatose. Temperature, 39.6; respiration, 64. Some rigidity of neck; no retraction. Pupils dilated; no strabismus. No Kernig's sign; no rosary. Lungs: Numerous very fine and medium scattered moist râles on both sides. Near the spine of the scapula on the left, respiration bronchial with dull tympanitic note on percussion. Liver felt 3 cm. below the costal margin; spleen not palpable. The forefinger of the left hand showed swelling of the first phalanx due to bony thickening (dactylitis). Eruption: At the middle of the right forearm, on the extensor surface, the skin was reddened over a circular area 8 mm. in diameter and covered with coarse scales. On removing these the skin beneath was found smooth and red, with no ulceration and no central hollow. The skin was infiltrated, but no definite nodule was felt. On the outer surface of the left leg, at the middle, were two similar lesions, 6 mm. in diameter. On the buttocks were several minute papules, 1 mm. in diameter, dull red in color, scarcely elevated above the surrounding skin. In the center a yellowish spot, but no definite umbilication.

The baby died April 28.

Autopsy (Dr. C. Hunter Dunn).—There was a profuse miliary tuberculosis involving the lungs, liver, spleen and omentum; tuberculous bronchopneumonia of both lungs; chronic tuberculosis of the mesenteric lymph nodes. Two of the larger skin lesions were excised, and both showed nodules in the subcutaneous fat tissue the size of large peas. Microscopic examination showed both nodules to be tuberculous. They were encapsulated and situated wholly beneath the skin. The latter was thinned and showed proliferation of the horny layer. One nodule was almost wholly caseated; one tubercle bacillus found within a giant cell. The other was in an earlier stage, with dense infiltration with lymphoid and epithelioid cells, chiefly the latter. Miliary tubercles were present but not sharply defined. There were fairly numerous giant cells and considerable caseation; three tubercle bacilli in three sections. The nature of the minute lesions on the buttocks could not be determined.

LITERATURE

While the tuberculous nature of lupus, scrofuloderm and verrucous tuberculosis was early discovered, it was not until quite recently that a group of dermatoses, to which the eruption I have been considering belongs, was recognized as bearing a definite relation to pre-existing tuberculosis in other organs. Hutchinson, in 1879, and C. Boeck, in 1880, were among the first to describe such cases, but the subject did not attract much attention until 1896, when Darier proposed the name "tuberculid" for one variety. This name has since been extended to cover the entire group of skin lesions associated with tuberculosis in other organs, but not obviously due to the tubercle bacillus itself. The original

definition specified that tubercle bacilli must be absent in the skin lesion, and that inoculation experiments must be negative. And, in fact, tubercle baciili have seldom been demonstrated in them. Hallopeau ascribes them to the action of toxins, and calls them "toxi-tuberculids."

The "papulo-squamous" and "papulo-necrotic" tuberculids of Darier and Boeck are apparently identical with the eruption which I have been describing. The disease is perhaps most generally recognized by dermatologists under the name of folliclis (Barthélemy) or acne scrofulosorum (Colcott Fox), but many other names have been given to it. Those interested in the subject will find a full discussion of the "tuberculids" in the symposium held at Paris in 1900[1] and in Jadassohn's article in Mracek's text-book.[2] The name "acute disseminated miliary tuberculosis of the skin" is assigned by Jadassohn to the eruption when it occurs in connection with general miliary tuberculosis, and should not be confused with localized miliary tuberculosis of the skin, a name rather unfortunately applied to ulcers about the mouth, anus, etc., of patients with advanced phthisis.

Most of the cases described by dermatologists were in adults, and not associated with miliary tuberculosis, but with chronic tuberculosis of the lungs or lymph nodes. Curiously enough, miliary tuberculosis in adults is seldom accompanied by skin lesions.

The eruption in infants was well described by T. Colcott Fox,[3] in 1895, under the name of acne scrofulosorum, but he did not recognize its tuberculous nature or its association with tuberculosis in other parts of the body. A few cases with miliary tuberculosis have been reported by Meyer, Leichtenstern and others.[4] A considerable proportion of these cases, in contrast to the findings in adults, has shown tubercle bacilli in the skin lesions. Until very recently the tuberculids have aroused little

1. XIII Congrès Internat. de Méd., Paris, 1900, Sect. de Derm. et de Syph., p. 95.
2. Jadassohn, J.: Mracek's Handbuch der Hautkrankheiten, iv, 256.
3. Fox, T. C.: Brit. Jour. Derm., 1895, vii, 341.
4. Bosellini: Gior. ital. d. mal. ven. e. d. pelle, 1904, p. 275; reference in Jadassohn's article, q. v.
Gaucher and Druelle: Jour. de mal. cutan. et syph., 1904, xvi, 108.
Hamburger, F.: Beitr. z. Klin. d. Tuberk., 1906, v, 197.
Hamburger, F.: München. med. Wchnschr., 1908, lv, 107.
Leichtenstein, O.: München. med. Wchnschr., 1897, p. 1.
Leiner and Spieler: Arch. f. Derm. u. Syph., 1906, lxxxi, 221.
Leiner, C.: In Pfaundler and Schlossman's Handbuch der Kinderheilkunde, ii, 2, p. 954.
Meyer, P.: Zwei Fälle v. metastat. Hauttuberculose. Inaug. Diss., Kiel, 1889.
Pelagatti, M.: Gior. d. mal. ven. e d. pelle, 1898, p. 704; reference in Jadassohn's article, q. v.
Rensburg, H.: Jahrb. f. Kinderh., 1904, lix, 360.

interest outside of the dermatologists. Last year, however, Hamburger,[5] from Escherich's clinic in Vienna, called attention in an excellent article to the frequency of the rash in the miliary tuberculosis of infants, and to its importance as a diagnostic sign.

In case I am correct in concluding that the infantile eruption is the same as that described in older children and adults under the name of papulo-necrotic tuberculid, folliclis, etc., there can be no longer any doubt that the latter disease is due to the action of the tubercle bacillus itself, and not to tuberculous toxins.

In spite of the fact that all of my cases in children have proved fatal, it is probable that instances will be found in which recovery takes place, particularly in older children. The fatal result in infants is probably only another manifestation of the more pernicious course of tuberculosis in general in the first years of life. In adults a complete cure of the tuberculid has followed excision of the primary focus (tuberculous lymph nodes).

CONCLUSIONS

1. There occurs frequently in miliary tuberculosis of infants and young children a specific eruption which is of great diagnostic importance. It is seen sometimes in patients who do not show a tuberculin reaction, and when present is of greater prognostic value than the positive tuberculin reaction, which occurs in a large proportion of all children from the lower classes (von Pirquet). The eruption in question, on the other hand, indicates almost certainly a fatal outcome.

2. This eruption is due to the deposit of tubercle bacilli in the skin. The bacilli reach the skin by means of the blood current.

311 Beacon Street.

---

5. Hamburger, F.: München. med. Wchnschr., 1908, lv, 107.

SOME PROBLEMS IN IMMUNITY AND THE TREATMENT OF INFECTIOUS DISEASES*

PHILIP HANSON HISS, JR., M.D.
NEW YORK

SOME FUNDAMENTAL FACTORS OF PATHOGENICITY AND INFECTIOUSNESS

If the animal body and the bacteria were absolutely fixed in their physiologic characters, varying in these neither qualitatively nor quantitatively in the adaptive sense when brought into contact with each other, it would probably be a much simpler matter than it is, to determine by careful study and experiment the exact factors underlying the conditions of pathogenicity and infectiousness of micro-organisms, and the reasons for the weakness or strength of the body when invaded by them, and we might thus, from a knowledge of the physiology of any given animal and bacterium, prognosticate the result of their activities, the one on the other. While this, of course, is not the case, still there are certain more or less fundamental requirements which experience has taught us must be met by an organism to be infectious for any given animal, and by infectious I mean the ability of an organism to live and multiply in the animal fluids or tissues. For instance, an organism which is shown not to grow at the body temperature of warm-blooded animals may safely be assumed not to be infectious for such animals; and experience is gradually teaching us that strictly aerobic organisms, those thriving only in the presence of free oxygen and not able to obtain this gas in available combinations from carbohydrates, can also safely be excluded from the infectious class. We have also learned that anaerobic organisms, although infectious when gaining entrance to tissues not abundantly supplied with blood, are practically unable to multiply in the blood stream and give rise to generalized infections.

There are few facts such as these, however, which, once in our possession, gained from a study of the organism apart from the animal body, form the basis for opinions as to the entire exclusion of organisms from the infectious class or as to the restriction of these organisms to certain body regions during the life of the infected animal, and which give us by simple cultural experiments and knowledge of the effect of physical

*Delivered before the Harvey Society, Feb. 6, 1909; from the Department of Bacteriology, College of Physicians and Surgeons, Columbia University, New York.

environment an idea as to the possible infectiousness or non-infectiousness of the organisms under consideration.

Most of the other factors determining infectiousness or the distribution of organisms in the animal body must be worked out in each case by actual animal experiments, and even after years of experimentation many of these factors are little known, for researches have demonstrated that bacteria showing little or no difference in their physical and chemical requirements under cultivation differ widely in their effects on the same animal economy, and that even the same organism may vary from time to time in its effects on the same species of animal; so that it is obvious that pathogenicity or even infectiousness is not an incondionate character of all germs or even of those known to have been pathogenic.

FACTORS OF AGGRESSION AND DEFENSE OF THE MICRO-ORGANISMS

It is my desire to focus attention for a while on some of the facts which have been worked out in regard to the chief factors of aggression and defense of the micro-organisms, leaving aside for the time being the special animal body in which these may be active or, indeed, alone called forth, and assuming that the organisms possess all of the obviously requisite characters for the rôle of infectious germs.

In the first place, I think, it should be made clear that infectiousness and pathogenicity are not synonymous terms. An organism may be exquisitely infectious—or, possibly better, parasitic—for a given animal, and yet its pathogenic effects may be of extremely slow development or almost *nil*, while another germ may be extremely pathogenic and yet little adapted for the life of infectiousness or parasitism; the very fact of its non-adaptation may apparently, in some instances, be the cause of its pathogenic action. Other organisms may have both requisites for the struggle with the opposing animal forces.

To understand more fully this point of view, it is necessary briefly to recall certain facts which are known about the physiology, metabolism, and composition of the bacteria, and of their ability to neutralize directly or to respond adaptively to the agents directed against them by the invaded animal. Some of these facts are so well known that passing mention alone is sufficient: such, for instance, is the fact that certain micro-organisms, especially the bacilli of diphtheria and tetanus, secrete soluble poisons both during artificial cultivation and during their life in the animal body, which poisons are eminently toxic. These poisons are true secretions and are largely independent of the composition of the surrounding medium so long as this favors the physiologic activities and

growth of the germs. Such germs, then, once having gained even an insecure foothold in the animal body, by no matter what favoring circumstances, are possessed of a powerful weapon of offense against the sensitive physiologic bases of the host, and of defense against its more immediate and mobile means of combating the germs themselves. In the case, however, of most other pathogenic bacteria, the secretion, at least in artificial media, of such highly soluble and potent poisons has not been demonstrated satisfactorily, although certain investigations point fairly conclusively to the production of some minor bodies which have been shown to act deleteriously on the red blood cells and on the leucocytes—the hemolytic, leucocidic and leucolytic substances which are looked on as probably true soluble toxins, like the toxins of diphtheria and tetanus. Other investigations support the idea that there may be still other true toxins secreted by these organisms, which also give rise in the animal body to the production of true antitoxins; i. e., which are found to be neutralized by their antisera, unit for unit, according to the law of multiples, just as are diphtheria and tetanus toxins.

Other minor poisons may in some instances be demonstrated in culture media, and also may possibly be formed in the animal body by the metabolic activities of the germs. These are either simply waste products of metabolism or bodies due to the decomposition of the nutrient media in which the germs are growing. These bodies are usually referred to as ptomains, and differ entirely from the true secreted toxins, both in their chemical composition and in their physiologic action, resembling in both of these the alkaloids. They are not known to give rise to antibodies of any kind in animals. Apart from all the poisons just mentioned; i. e., the toxins, hemolysins, lecocidins and ptomains, there is supposed to exist a most vitally important and interesting group of poisonous substances, the so-called endotoxins. These, so far as our knowledge goes, are poisons rather firmly seated in the bacterial cell, which are not secreted in our ordinary cultural media, and are supposed by most observers not to be separable in the animal fluids and tissues from the intact bacterial cell. These poisons may be demonstrated in old cultures, in which the bacteria are dead and disintegrating or undergoing autolysis—although Pfeiffer does not consider autolytic products necessarily similar to endotoxins—or they may be obtained by destroying the bacteria mechanically by pressure and grinding, or by breaking them while frozen. In the animal body they are said to become free when the bacteria die and decompose or are disintegrated by the digestive bodies by which they have been attacked. These endotoxins are recognized by the fact that they

do not call out true antitoxins which become free in the plasma and serum, but do, nevertheless, lead to the formation of digestive antibodies, these not following, however, the "law of multiples" in protecting infected animals from the poisons. The liberation of these poisons by the destruction of bacteria in the animal body is best illustrated by the so-called phenomenon of Pfeiffer which takes place when cholera vibrios and immune cholera serum are introduced into the peritoneal cavity of a guinea-pig. If specimens are withdrawn from time to time from the peritoneal cavity of an animal so treated, a rapid swelling up, disintegration and disappearance of the vibrios can readily be demonstrated. The organisms apparently do not multiply in the animal body under these conditions and are almost immediately destroyed. This disintegrating power is also claimed for the body fluids of normal animals and is supposed to be demonstrated by the following experiment. When graded quantities of a fresh cholera culture are introduced into the peritoneal cavity of normal guinea-pigs of equal weight, the following phenomena can be regularly observed: Minimal doses of the culture produce a febrile condition which continues for a few hours with no serious symptoms. Slightly larger doses give rise, after a short interval, during which there is fever, to a marked drop in temperature and definite symptoms of cholera poisoning—muscular weakness, twitching and general prostration. These symptoms of poisoning then gradually disappear, and after twenty-four hours the guinea-pigs are again normal. If the quantity of cholera culture injected is carefully increased up to the minimal lethal dose, the animal dies with all the symptoms of cholera intoxication, but on autopsy the peritoneum is found to be entirely sterile, or only a few isolated cholera spirilla are found, usually inclosed in pus cells. Finally, if larger quantities of living cholera spirilla are injected, the peritoneal cavity shows a profuse, serous, sometimes hemorrhagic exudate, which contains innumerable actively motile micro-organisms. The point of interest in this experiment is the demonstration of the fact that the normal guinea-pigs which receive enough of the cholera vibrios to prove fatal have destroyed the vibrios and presumably died from the poison thus liberated, and not from poisons secreted by living vibrios, or from an overcoming of their systems by the rapid multiplication of the organisms. It is only when the animal system is previously flooded with an overwhelming dose that the vibrios are found alive and multiplying even locally in the peritoneum after death. This does not mean, however, that no multiplication ever goes on hand in hand with the destruction of the germs in the infected animal; on the contrary, such a multiplication is probably the rule

rather than the exception, as has been shown fairly conclusively by the experiments of Radziewsky, and was beautifully illustrated by an experiment of Pfeiffer and Wassermann, who after having shown that the blood serum of human beings who have recovered from Asiatic cholera has the power to protect guinea-pigs from ordinarily fatal doses of cholera spirilla, even when used in high dilutions, then proved that this protective power is not an antitoxic one, but depends largely, if not entirely, on the ability of the serum to aid in the immediate dissolution of the vibrios. Thus animals which received only a fraction of a milligram of such a serum were able to bear the injection of a loopful of virulent cholera vibrios, practically without reaction, while control animals succumbed to one-fourth of the dose with typical symptoms. Now, however, if the dose was increased to three or five loopfuls, not even ten thousand times the original amount of the serum would protect the animals against the inoculation. The toxic effects may, in fact, as shown by Pfeiffer, appear with extraordinary rapidity, so that in these animals the temperature may show the lethal drop within two hours after inoculation, while control animals which have received the same quantity of cholera germs without the serum may show a similar lethal drop in temperature for four to five hours.

An explanation of the results of this serum is found, probably, in the fact that guinea-pigs are able to withstand a certain quantity of the intracellular cholera poison (endotoxin) which may be represented by one loopful of a fresh culture. If the animals are given smaller quantities without the serum, say one-fourth to one-half loopful, these may increase for a time without producing marked symptoms. Parallel with the increase, however, the phenomenon of germ destruction is going on and characteristic symptoms of intoxication appear at the moment when the number of vibrios destroyed has become so large that it corresponds to more than one loopful of the cholera culture. An animal will thus withstand a culture of any size when mixed with immune serum, if the dose does not exceed the limit of intoxication before it is entirely destroyed. On the other hand, when guinea-pigs receive the larger dose of three to five loopfuls, the serum, not being antitoxic, is not able to counteract the fatal effects of the liberated cholera poisons, but, on the other hand, enormously increases the rate of destruction of the vibrios, and hence intoxication appears earlier in such treated animals than in the controls receiving the organisms alone.

I have selected this classic cholera experiment because I feel that it illustrates the most extreme limit of the endotoxin point of view, and,

further, because the cholera organism, standing at one end of the scale, is the most extreme example of pathogenicity by virtue of its own destruction, while the diphtheria bacillus at the other end is one of the classic examples of pathogenicity by virtue of secreted toxins. Neither of these organisms is truly invasive or highly parasitic, and both are harmful usually by the action of their poisons alone and acting, as it were, from a base of supply on the periphery of the animal system. Between these two extremes stand all grades of infective germs.

These two organisms are typical examples of their kind, but there are few organisms which secrete such highly toxic soluble bodies as do diphtheria bacilli, and there are few so susceptible as the cholera organism to disintegration within the animal body; and yet there are many germs which are extremely pathogenic, and in many cases capable of severely and detrimentally infecting the animal body. In view of this unquestioned fact, I am of the opinion that the teaching which considers all poisonings as due either to true soluble secreted poisons, or to true endotoxins liberated only on disintegration of the bacterial cell, is too narrow; and it would seem probable that many organisms, possibly all, secrete bodies which are not soluble in their condition at secretion in culture media or in the body fluids, but which are susceptible to digestion in the animal body, and may thus become soluble and assimilable, and when toxic act harmfully on the body cells. This question is an important one and I shall speak of it later. Besides these actively poisonous bodies which we have been considering, there are probably bodies such as some at least of the bodies called aggressins by Bail, which, while not being toxic in themselves for the animal body, nevertheless are active defensive agents of the bacteria, probably neutralizing certain bodies of the animal economy, which are indirectly injurious to the bacteria. Further than this, certain bacteria may be furnished with envelopes, capable possibly of protecting them either chemically or physically from harmful influences.

In thinking over these questions I have gained some clarity of conception, based on visual perception by comparing some of the products of pathogenic bacteria with bacterial pigments and with insoluble interstitial or intercellular substance, which may be seen accompanying bacteria in cover-glass preparations. Soluble toxic secretions are to be compared to such pigments as the pyocyanin of *Bacillus pyocyaneus*, which is so readily soluble in culture media; endotoxins proper to pigments confined to the bacterial cell, or at least when secreted, being insoluble in culture media, such, for instance, as the well-known red pigment of

Bacillus prodigiosus, which may often be seen free among the bacteria in irregular red granules like carmine powder. That bodies such as this latter might be extruded from pathogenic bacteria, and not be soluble in the usual culture fluids, is not improbable, and the fact that more or less insoluble interstitial substances are not infrequent among bacteria is well known. Among pathogenic germs these characters, in my experience, are usually, if not always, more marked in freshly isolated cultures. The sticky, almost slimy character of cultures of meningococcus may be recalled, a character which tends to disappear after a few generations of artificial cultivation, and the highly mucinous capsule of the *Streptococcus mucosus* which tends to decrease under artificial cultivation, as do also the capsules of pneumococci and streptococci.

Now, it seems to me—and this view has been supported by Walker, Deutsch, Welch, and Eisenberg, and is, in fact, but an axiom which would be recognized immediately by any trained biologist—that all micro-organisms will adapt themselves so far as is permitted by their physiologic peculiarities to the stress of the environment, the exact direction which this adaptation will take being determined by the character of the environment, chemical and physical, and the physical, chemical and physiologic characteristics of the germ involved.

Thus we might have a germ increasing its toxin output in the face of neutralizing stimuli. Or we might have germs which are more especially opposed by lytic bodies, either increasing their receptor apparatus, as has been claimed by Pfeiffer in the case of virulent cholera organisms; or a more efficient protection can be conceived in the formation or increase in thickness and impermeability of surrounding envelopes, or extruded neutral substances, which are not soluble, but remain adherent to the germs. Eisenberg has developed this latest idea in his ectoplasm theory, and, indeed, it has long been recognized that capsule formation may be simply a response to unfavorable environment and a more or less efficient attempt at protection. It is certainly true that a number of our most highly adapted invasive germs, such as anthrax, pneumococcus, and the organisms of the hemorrhagic septicemias, do develop capsules in the animal body; and the most virulent strains, it appears, have this formation most highly developed.

The fact also that many of the non-capsule-forming organisms appear larger in the fluid of fatally infected animals lends some support to such a view.

DEFENSIVE FACTORS OF THE ANIMAL ORGANISM

Thus far, in considering the means of offense and defense at the command of the bacteria, we have largely left out of consideration the animal organisms against which these are directed in an adaptive way, or by the changes in whose functions, metabolism, tissues, cells, and fluids, we are largely made aware of their existence.

The internal defenses of the animal body—and with these alone we are concerned—have largely been elucidated through morphologic investigation of cellular activities taking place in the animal body or under controlled conditions in the test-tube, and by visible reactions taking place in test-tubes between the fluids of normal or immunized animals and the bacteria and their products, and, finally, by the more purely physiologic tests of the protecting power and mechanism of action of animal fluids or extracts when introduced into another animal of the same or different species, along with the bacteria or their products.

Such studies have, as is well known, afforded a vast amount of information. Through them the soluble secreted bacterial poisons have been demonstrated and have been found to stimulate the production of neutralizing bodies, the antitoxins; bacteria and their culture filtrates have been shown to call forth bodies which are present in the serum of animals treated with them, and which cause a precipitation of certain bacterial constituents of the filtrate—the precipitins; and injections of animals with bacteria or their products have been found to cause the production of bodies which are present in the serum and which have the power of agglutinating the bacteria when brought into contact with them—the agglutinins; and other bodies are likewise produced which are capable under proper conditions of killing the bacteria—the bactericidal substances—or even of dissolving them as we have seen in some instances—the bacteriolytic substances. All of these bodies may be demonstrated in the serum of certain normal animals and may be shown to be increased during the immunization of these animals with bacteria or their products. The complementing body, however, which is necessary for the activation of the bactericidal and bacteriolytic bodies is not known to be increased during immunization, at least so far as its presence in the serum is concerned.

These facts we have learned from the study of the serum; on the other hand, the morphologic investigations instigated and carried on largely by Metchnikoff and his followers have taught us the great part which the formed elements of the blood and lymph play in the protection against and cure of germ diseases, and the importance of the polymorphonuclear

and large mononuclear leucocytes as phagocytes is now widely recognized.

Of these cells, the polymorphonuclear leucocytes take a very active part in the ingestion and destruction of bacteria, while the large mononuclear leucocytes and endothelial cells, especially those lining the blood vessels and body cavities, although also able to ingest bacteria directly, are chiefly active in taking up cells of animal origin, principally those which necessarily, in the normal course of events, belong to the same animal and have probably become injured or have suffered death.

It is not, in this connection, to my mind, a far-fetched idea to suppose that phagocytic cells may depend naturally on other cells and bacteria as a part of their regular food supply. The polymorphonuclear leucocytes may thus depend to some extent on the ever-entering bacteria and their remains; for, as we know, bacteria are constantly entering along the regular channels of absorption; and it is just as obvious that numbers of blood and tissue cells are constantly dying out and must be disposed of, for such processes are always in evidence in the spleen, and the ingestion of polymorphonuclear leucocytes by the large mononuclears can be observed wherever leucocytes are collected in exudates, due either to infections, poisons, or supposedly benign irritants. The simple fact that these cells retain the basic physiologic activities and an ability to ingest and digest food in its crudest form, which ability was the heritage of their free-swimming ancestors, and that they have not suffered the total specialization and physiologic degeneracy of the fixed tissue cells, is sufficient evidence to my mind to warrant the conclusion that they are the most active factors in the protection of the specialized internal tissue cells, which control the general metabolism and higher functions of the animal body. I would call attention here to the fact that the leucocytes, alone probably of all the true cells of the body, are entirely independent of the nerve control, are subject alone to the stimulation of their chemical and physical environment, and are thus susceptible of adaptation to various purposes which would be fatal to the duties of cells controlled by the nerve mechanism for the special functions of the organism at large. Further than this the death of leucocytes does not matter, as would the death of specialized and nerve-controlled cells, for no special metabolic or functional derangement occurs from their destruction.

By citing this independence of the leucocytes I would not have it understood that they have not varied from primitive ameboid cells, for undoubtedly their life and proper functioning is largely determined by the special plasma in which they live, and it may be that their food,

although at times crude compared with that of the other body cells, is nevertheless often prepared for them by processes going on in the plasma.

Questions relating to the independence and to the interrelation of the plasma and leucocytes in their action on invading micro-organisms and the action of plasma as compared with serum have been ground for scientific strife for many years, one side hotly contending for the activity of the plasma, the other for the activity of the phagocytes; the humoralist at first neglecting, if not absolutely forgetting, that a fluid can not be self-replenishing, while the supporters of phagocytosis largely overlooked the fact that plasma is not necessarily an inert menstruum such as salt solution.

While these differences have been to some extent adjusted by the theory and work of Ehrlich, an immediate point of contention is still the question of the similarity of action of plasma and serum. The humoral school contends that the alexin of Buchner—complement of later writers—is secreted into the plasma, while the Metchnikoff school claims that it is only given up from injured leucocytes in the body, and to the serum during coagulation. The Metchnikoff school admits, however, that the amboceptors necessary for bactericidal and bacteriolytic action are formed in excess in the phagocytes, and given off from these to the plasma, yet asserts that they are inactive for lack of the complement which is normally retained in the leucocytes, and that they simply prepare the bacteria for complete digestion in the leucocytes. The relation of the bacteriolytic amboceptors to intracellular digestion is not settled, although it seems illogical for a digestive body to be produced in excess that has not arisen from cells by the stimulation of its use, and, as the leucocytes take up the bacteria, they are the most likely producers and users of this body.

In 1894 a further adjustment of differences took place, when certain phenomena observed by Denys and his pupil Leclef demonstrated that the act of phagocytosis when performed in serum, in some instances at least, was dependent on the presence of substances in the serum. Thus they were able to show that leucocytes removed from normal blood and placed with bacteria in immune serum engulfed the bacteria actively, while leucocytes from immunized animals mixed with bacteria in normal serum took up the organisms no more actively than the normal leucocytes. The bodies inciting the phagocytosis must obviously, then, they concluded, be in the serum. Whether these bodies acted on the leucocyte or on the bacteria was not then determined, but Denys concluded, in 1898, that the bacteria were directly affected. The fact that the action is exerted on the

bacteria was recently determined positively by Wright for normal serum, and by Neufeld and Rimpau, independently of Wright, for immune serum. These bodies have been called opsonins by Wright, and bacteriotropins by Neufeld, and have been shown to attach themselves to the bacteria and thus prepare them for ingestion by the phagocytes. It has also been shown by various observers that the more virulent the germ, the less susceptible it is to phagocytosis and the more potent the antisera must be to permit of the ingestion by the cells.

If now, for clarity of conception, we summarize briefly the disease-producing agents possessed by the bacteria and the opposing substances of the serum and processes of the animal body, we find the true toxins, including probably leucocidins and hemolysins, opposed by antitoxins which become free in the plasma; the bacterial bodies and probably the endotoxins opposed by leucocytes, and possibly directly in the plasma by lytic substances formed of amboceptor and complement, which either kill or dissolve the bacteria and free the endotoxins, but do not neutralize them; and, third, we have probably certain secretions which oppose the opsonins, and thus prevent phagocytosis—antiopsonins—bodies which may possibly be the so-called aggressins of Bail, and which are present in exudates and, although not toxic in themselves, increase the infectiousness of the bacteria with which they are injected; and, finally, opposed to bacteria and their broth filtrates we have the agglutinins and precipitins, the activities of which are manifest in serum, but whose relation to immunity is not altogether obvious, as they have not been shown satisfactorily to bring about agglutination or precipitation in the animal body.

While all of these different functions and chemical substances are possessed by animals as a class, it is becoming more and more obvious that these are not always present or active in the same degree, and that there are recognizable differences in the protective mechanism of different animal species—in species, in fact, not far removed from each other in the natural classification. An explanation of reactions to a given infection which applies in the case of one species is not, therefore, obviously applicable in the case of another species. This is true not only of the mechanism of protection as it takes place in the serum of different animals and in their plasma, but also of phagocytosis and phagocytic digestion and the factors which contribute to the perfection of these processes. The constant stumbling-block in the way of a correct interpretation of processes going on in the animal body is our inability, as we have seen, to argue from serum phenomena to phenomena occurring in the plasma.

A failure to keep this in mind, although it is fully recognized, has undoubtedly led to many hasty conclusions, particularly connected with the theory of lytic immunity. Let me illustrate this with a well-known example: Fresh rabbit serum is actively germicidal for anthrax bacilli, dog serum is not; yet rabbits are extremely sensitive to a true anthrax infection, while dogs are very resistant. Experiment has shown that there are lytic amboceptors in the sera of both these animals, but that the dog's serum does not contain the complement necessary for their action on the bacilli; the complement presumably has remained in the body cells, whereas in the case of the rabbit it has possibly been liberated from the leucocytes during clotting. The reason the dog is insusceptible is, then, not because of a more active plasma destruction of the invading anthrax germs, but because of a more perfect adjustment of the cellular mechanism to the infection, although if we simply followed the theory of the bactericidal action of serum and plasma as being coextensive, and the active protective mechanism, the rabbit should have been protected, while the dog should have succumbed. The difference probably resides in the possession of all requisites for the perfect performance of phagocytosis, and the complete digestion of the bacteria by the phagocytes of the dog, while in the rabbit either the mechanism of ingestion is incomplete or the cells fail to cope successfully with their contents after ingestion. This example has been selected because anthrax bacilli have been shown to contain less toxic intracellular bodies—endotoxins—than many other infectious germs, and the likelihood of the rabbit being poisoned by any primary plasma disintegration of the bacilli is not very great, so that if the plasma mechanism had corresponded to that of the serum the animal should have been saved. The validity of such an argument would not have been so apparent if we had substituted cholera vibrios for anthrax bacilli in rabbits, for the bodies liberated from cholera bacilli at their disintegration are very toxic.

Even if we were willing to admit on the evidence so far in our possession that the bactericidal and bacteriolytic bodies which are present in the sera of various animals are present and active against certain micro-organisms in the same manner in their plasma, we should, nevertheless, still have a number of micro-organisms which are singularly insusceptible to such action of the sera or plasma, even of animals highly immunized against them. The method of resistance against these would have to be explained by a different mechanism, and I do not wish to include here simple insusceptibility to the action of their poison, but an actual destruction of the bacteria and their poisonous products. Now,

if this death and destruction is not accomplished in the plasma, then, unless we postulate a direct excretion of the bacteria by the liver or kidneys, for instance, an occurrence which is really a pathologic phenomenon, not a process of cure, we must look largely to the activities of the leucocytes for its accomplishment.

The serum substances which further leucocytosis have, as we have seen, received much attention of late, and the bodies antagonistic to the bacteria which are supposed to be contained in the leucocytes have also been extensively investigated.

Experiments bearing on these questions make it appear extremely probable that bactericidal and digestive action depend on two processes; one of these is the bacteriolytic action of the serum and plasma, the other the bactericidal action of substances retained in the leucocytes. As an example of the type dependent solely on the bactericidal substances of the serum or plasma, the mechanism of the natural and artificial immunity of guinea-pigs to typhoid and cholera may be cited, since in these animals no one has as yet succeeded in demonstrating that substances derived from the leucocytes by extraction have any bactericidal action on the organisms of these two diseases. This does not mean, however, that the bactericidal action takes place naturally outside of the leucocytes, for the bacteria loaded with amboceptors are probably taken into the leucocyte and there digested. As examples of immunity depending on the bactericidal substances of the leucocytes, the natural and artificial immunity of dogs and cats to anthrax, and the immunity of guinea-pigs to certain strains of proteus, may be cited, for in these cases the leucocyte extract is germicidal, the serum is not.

Stated impartially, then, our knowledge of immune bodies and processes stands somewhat thus: Bodies which are bactericidal and bacteriolytic may be present in the plasma, and certainly in the serum, wherever this is formed in a pathologic process, which when supplied with complement, either normally present in the plasma or derived from injured leucocytes, may be active against micro-organisms, either killing them or actually breaking them up in some cases and liberating bodies which are then directly poisonous or become so by further digestion. Beside these germicidal bodies, there are other bodies which, while not directly harmful to the bacteria, render them powerless against the phagocyting power of the leucocytes. These bodies are probably present in the plasma, certainly in the serum. They are the opsonins or bacteriotropins.

After phagocytosis has taken place, the germs may be killed and digested. Some of the bactericidal bodies of the phagocytes are bodies

differing in character from the lytic bodies of the serum, and are either not given off to the serum or are not active in it; but there is no proof that the lytic amboceptors present in the serum are not normally derived from the leucocytes, and active in intracellular digestion when activated by complement. This is supported by the supposition that guinea-pig leucocyte extracts are not germicidal for cholera and typhoid organisms. Nevertheless, intracellular digestion of these germs does go on; it is likely, therefore, that the amboceptors present in the plasma, whatever their source, attach themselves to the germs and aid in intracellular digestion.

None of the processes just mentioned leads to the formation of antitoxins which become free in the plasma or serum. Now, in view of these facts and suppositions, I believe that it is logical to conceive that nearly all pathogenic germs secrete bodies which are not readily soluble in culture fluids or in the fluids of the animal body; that these bodies are not readily, if at all, assimilable by non-phagocyting cells. These bodies may, however, be broken up by digestive bodies present in the serum, and from them may thus be liberated a poisonous body, which may then be assimilated by the higher cells of the body, and, when in sufficient quantity, cause death. The more rapid the process of liberation the more quickly death ensues. This plasma digestion is, then, according to my conception, a mechanism which is faulty when applied to bacteria. I conceive that the fault occurs somewhat as follows: Bacteria and their insoluble or non-assimilable products when taken into the phagocyte are subjected to two processes, a primary bactericidal and coagulating one, and then a more leisurely lytic or disintegrating action, during which poisonous products are probably liberated, but slowly enough to be taken care of by neutralizing bodies. Even if the leucocyte dies, it is usually promptly taken up by a mononuclear cell, and the poisons do not become free in the fluids. Now, in this process the only bodies which are produced in excess and at the same time are capable of escaping from the leucocytes are the lytic bodies; neither the toxin-neutralizing body nor the coagulating body are secreted or given off from the cell. Such lytic amboceptors, then, when present in the plasma and activated by complement, may become an active agent for harm by liberating poisonous substances from the bodies of germs which are susceptible to such action, or from the insoluble or non-assimilable products of these or more lysis-resisting members of the invasive organisms; and by the action of these poisons, phagocytosis may be hindered and the specialized cells poisoned. Since the neutralizing or coagulating bodies are not present in the

plasma, the leucocytes are then poisoned from without, just as are the specialized cells, and the more active the plasma digestion the more deranged the true protective mechanism becomes.

I have gone thus somewhat lengthily, but nevertheless in an outline manner, into some of the problems of immunity, particularly those relating to the micro-organisms which are harmful to the animal body, not so much through their ability to secrete harmful soluble poisons, as through their insistently invasive character, or by the liberation of the toxic products resulting from the destruction of their secretions or of their own bodies. It is the diseases caused by these organisms on which I now wish to center attention.

The organisms of these diseases undoubtedly belong to two or more classes, in one of which I would place the typical septicemia producers —anthrax, pneumococcus, streptococcus, etc.—in the other the non-invasive organisms, typified by cholera and to some degree by typhoid. Between these two extremes there are all grades. The bacillus of tuberculosis, I think, stands by itself and offers a most special problem.

If I have made myself at all clear in setting forth some of the data amassed in the study of these types of micro-organisms, and of the processes supposed to be involved in meeting infection and establishing cure and immunity from them, I think you will comprehend more readily some of the problems which daily face us in our struggle to arrive at a rational method of biologic treatment, and realize more fully, in the light of this knowledge, why disappointment has so persistently followed in the wake of serum therapy. For, in spite of the most persistent attempts to produce curative sera, the results have not been satisfactory and have not led, except in rare instances, to the practical use of such sera in the treatment of disease in man.

The sera, thus produced, have not, except in a very minor way, been antitoxic in the usually accepted sense, and depend, as we have seen, probably, for any protective value they may possess, on their germicidal and bacteriolytic power and on the opsonins they may carry, and thus facilitate phagocytosis. These sera are capable of protecting an animal from a many times lethal dose of an infecting organism, when mixed with it in surprisingly minute quantities; but that any consistent curative effects, other than merely local, have been definitely determined as due to their action, after an infection has once been established, may justly be questioned.

On the other hand, indeed, test and experiment have shown that animals and man suffering from a true infection may and often do

themselves furnish sera capable of strong bactericidal and bacteriolytic action (when combined with normal sera containing complement), and yet, in spite of this, they succumb or may be subject to severe relapses.

In the light of these and other facts which have been cited, it has long seemed to me that one might well refrain from attempts to produce beneficial effects by injecting still further amounts of bacteriolytic or similar bodies, and seek further for an explanation of the exact methods and processes of the cure effected in those animals and man who do survive an infection.

Failure to solve these problems on lines hitherto followed should not discourage us, however, while we know that animals and man do recover naturally from such infections and that the mechanism of the animal body suffices to protect the animal even against enormous doses of injected organisms, without serious histologic changes or marked systemic symptoms, if these organisms be given at proper intervals and in gradually increasing amounts. The conclusion that this power must reside in increased digestive and neutralizing or poison-destroying powers of the animal organisms can not well be avoided, and these functions of the animal mechanism will probably be found to take place largely in some group of cells.

The animal body, then, ideally protected in the time of bacterial invasion, may well be one in which some set of cells—phagocytes—are immediately ready and able to take up the bacterial invaders and destroy them, and within their own bodies to neutralize any poisons secreted by such invaders or arising from their destruction by digestion, and this without serious harm to the ingesting cells; or—failing this full immunity from serious harm—it may be that these ingesting cells are, in their turn, taken up and, with their noxious contents, digested by other scavenging cells, with a minimum liberation of the substances which could injure the body cells dedicated to specialized functions. And I believe that the whole struggle of the infected organism may be summed up as a conflict between the leucocytes and the germs, and that it is an attempt to bring the invading germs within the leucocytes, and is a process with which the system at large often has little or nothing to do, except as an innocent and injured bystander, and that extracellular destruction of bacteria and toxicogenic bodies is an untoward event often leading to dire consequences, and depending on the chance occurrence of suitable digestive bodies in the serum which have been thrown off in excess from the cells, and may thus become a menace to the system at large by liberating poisonous bodies from comparatively harmless compounds.

Thus, in many instances, it seems to me, we are probably dealing with an immunity, a large part of the mechanism of which is individually cellular, not only in the sense of phagocytosis and digestion, but in the neutralization or destruction of poisons which arise from the disintegration of the bacteria and their products—a mechanism in which the protecting cells *must* intervene and, unaided by antitoxic bodies in the plasma, neutralize within themselves the poisonous products of the invading micro-organisms.

It was this thought which suggested to me the idea of treating disease by aiding the leucocytes by furnishing them as directly as possible with the weapons which were being taken away from them in their fight with invading micro-organisms, and to protect them thus from destruction and give them an opportunity to recuperate and carry on successfully their struggle against the invading germs. These weapons, whatever might be their nature, I assumed might possibly be furnished by an extract of the active substances of the leucocytes themselves—substances not ordinarily given up to the plasma or serum—and I also assumed that extracts would be more efficacious than living leucocytes themselves, introduced into the infected animal, since, if diffusible, they would be distributed impartially to all parts of the body by the circulatory mechanism and, as quickly as absorption would permit, relieve the fatigued leucocytes and protect, by any toxin-neutralizing or other power they might possess, the cells of highly specialized functions.

This idea of immunity differs from one that simply assumes the cells as the source of all immune bodies in that it takes into consideration the presence and production in the leucocytes of agents which are not normally given up to the plasma, but which are constantly able to reproduce themselves and carry on the functions of coagulation, of digestion, or of neutralization simply for the benefit and protection of the individual cell, while not being secreted or excreted by the cells for the more general benefit of the cell community at large.

It seems to me, then, that when these sources of protection are overtaxed or fail to act efficiently on account of some inherent weakness or untoward circumstance of location, the most reasonable course is, if possible, to support the chief army of attack, by introducing into the infected animal or man the *substances* composing the chief cells or all the cells of an exudate from normal or immunized animals in the most available and diffusible form, as little changed by manipulation as possible. The extracts of exudates from previously immunized animals might better serve this purpose than those from normal animals, since their

cells probably have in their fight against the same organisms gained increased powers, as is evidenced by the ability of such immunized animals to dispose safely of immense numbers of organisms without serious harm or loss of weight. As this might, in part, however, be due to bodies in the fluids causing more rapid and complete phagocytosis, a further adjuvant, immune serum, might be found serviceable in some cases, especially if it were an anti-infectious or opsonin-containing serum.

In carrying out this idea in our tests, not only polynuclear leucocytes, but also extracts of spleen and of mononuclear leucocytes have been experimented with, not only because they might be found to have a toxin-neutralizing effect, but because observation has shown that mononuclear leucocytes are active in engulfing certain organisms, such, for instance, as the bacilli of tuberculosis and certain organisms giving rise to chronic infections, and also parasites of animal origin.

It is obvious that such a scheme of experimentation is a broad one, and that some of its phases have been attacked from various sides by other workers.

Most of the workers have been chiefly interested, apparently, in elucidating the direct germicidal action of certain leucocyte extracts on bacteria, and in bringing out differences between the serum alexins and the bactericidal bodies of the leucocytes—in other words, with the visible mechanism of the bactericidal activities of leucocytes as shown *in vitro* and in the peritoneal cavity.

Attempts to influence infection by the use of organ extracts have also been made, apparently with little success. The thought, however, underlying most of this work differs from my own, as these experimenters have adopted such a course, arguing that certain organs may be the source of true antitoxins, or of the so-called immune bodies—amboceptors—and simply contain them in greater quantity than does the serum.

My work, on the other hand, as I have endeavored to make clear, is based on another conception, and has had as its immediate object the practical determination of the *curative* effects of such extracts.

THE TREATMENT OF INFECTIONS IN ANIMALS WITH LEUCOCYTE EXTRACT

Passing, now, from these questions of theory, I will outline briefly the result of the treatment of infections in animals with leucocyte extracts. These infections or poisonings have usually been brought about by intravenous inoculations, and, as a rule, the treatments with extract have been given subcutaneously, although at times intraperitoneally.

The infections to which I wish to call your attention chiefly are: staphylococcus, streptococcus, pneumococcus, typhoid, dysentery, meningococcus and cholera, although we have also experimented with tuberculosis and with infections due to micro-organisms of animal origin—the spirochetes and trypanosomes—and with animals suffering from inoculable tumors.

It is evident that the extracts used must vary in strength, as there is no means by which they can be exactly standardized, principally on account of the red blood cells which are often present in the exudates.

I would call attention here to the fact that neutrophile granules of the rabbit cells apparently go into solution in water, the cytoplasm undergoing marked disruption, while the nuclei of the cells swell up and resemble the larger, paler nuclei of mononuclear cells, but by no means go into complete solution. It would not surprise me, therefore, if the constituents of the cytoplasm were active. What part the nuclei play in the outcome of experiments is a question I am at present unable to answer, although I am not unmindful of the beneficial action claimed by various writers for the so-called nucleates (nucleic acids), especially in warding off peritoneal infections. They, however, refer this action to an increased leucocytosis. The sources of these nucleic acids are, however, so varied, being either from yeast or animal cells, that one might well, theoretically at least, look askance at the introduction of some of these bodies during the course of a disease already taxing the powers of the system.

Staphylococcus Infections in Animals.—If we analyze our series of staphylococcus infections,[1] we find that animals receiving subcutaneous injections of rapidly fatal doses of *Staphylococcus pyogenes aureus* can generally be saved by treatment with the extract of normal leucocytes of rabbits even in small doses, especially when these are given intraperitoneally. When intravenous injections are practiced, the results are different, but treated animals usually survive the controls many days and present modified histologic pictures.

Streptococcus Infections in Animals.—In experiments with streptococcus infections I have worked only with those brought about by intravenous injections. In these experiments we find a marked lengthening of life and even a survival of the treated animals, and better results in the animals treated early than in those treated late. All of the animals which lived long enough developed articular or periarticular lesions, which tend to distinguish these infections from pneumococcus infections,

1. Hiss: Jour. Med. Research, 1908, xix, 323. See this article for details of these and the following experiments on animals.

which, as we shall see, seldom or never give rise in rabbits to such localizations.

Pneumococcus Infections in Animals.—If, in my series of experiments on pneumococcus infections, we consider the animals treated with the extract of leucocytes of normal rabbits, we find that in such animals an infection, surely fatal in untreated rabbits, becomes significantly modified in treated animals, even if this treatment be delayed many hours. Thus, out of eight control animals used in four experiments in which the intravenous infecting dose was the same, all died, averaging only forty-five hours of life after being infected. Of the animals treated—some as late as twenty-four hours after infection—nine out of twelve survived the infection, three died with an average life of sixty hours after infection, two of them not having received treatment until the expiration of twenty-four hours.

These are not selected examples, but are records of events as they developed in our regular research tests, and have been fully confirmed by experiments undertaken in elucidation of other points, and are unmistakably indicative of the powerful beneficial action of such extracts on pneumococcus septicemia in rabbits.

On the other hand, living leucocytes, introduced subcutaneously, or even peritoneally, have little or no effect on systemic infections.

Typhoid Infections in Animals.—We find that typhoid infections, if indeed we may really call them such, in rabbits are essentially different from infections caused by such organisms as staphylococci, streptococci, and pneumococci. The animals seem rather to suffer an acute intoxication, from which they either die within a very limited time when organisms may be recovered from them, or recover completely, or go into a state of cachexia, but without organisms in the blood or organs. In my experiments the animals, as is usual after toxic doses of typhoid bacilli, showed signs of poisoning, remaining quiet and refusing all food for some hours. The animals receiving protection with leucocyte extract, shortly after this treatment, usually seemed worse than the control, and to the inexperienced would appear the most likely to die. This might possibly be due to a more rapid liberation of toxic substances by enhanced bacteriolytic processes, either brought about by a fuller complementing of immune bodies by the extract or to special digestive bodies of the leucocytic extract, or it might be due to a somnolent state following a relief from active poisoning. That the poisoning in reality was fundamentally less severe than in the more normal-appearing control is, however, shown

by the rapid return of the treated animals to normal condition and weight, the weights following a perfectly logical order—untreated animal, animal treated late, animal treated early, as is illustrated by the following examples:

	Untreated Animals.	Treated Within 5 hours.	Treated Within 1 hour.
April 8	1,125 grams	1,108 grams	1,104 grams
April 11	1,035 grams	1,114 grams	1,135 grams
April 12	1,030 grams	1,160 grams	1,200 grams
April 13	1,010 grams	1,125 grams	1,190 grams
April 15	1,085 grams (Injection.)	1,148 grams (Injection.)	1,225 grams (Injection.)
April 17	1,020 grams	1,130 grams	1,185 grams
April 18	1,000 grams	1,188 grams	1,250 grams
April 19	968 grams (Injection.)	1,160 grams (Injection.)	1,228 grams (Injection.)
April 22	935 grams	1,100 grams	1,135 grams
April 24	900 grams	1,100 grams	1,170 grams
April 26	865 grams	1,085 grams	1,210 grams
April 29	Dead.	1,070 grams	1,265 grams
May 1	——	1,140 grams	1,305 grams

In this experiment no organisms were alive in the control, so that the animal died from poisoning and interference probably with metabolism and excretion due to cellular changes.

In another experiment the dose of typhoid bacilli was so toxic that the temperature fell immediately instead of rising. The effect of the extract in the early treated animal was not a further lowering of the temperature, but an arrest and more abrupt rise than in the control and in the animal treated after five hours. Furthermore, both the control and the later treated animal had bad diarrhea within two hours, but the animal treated in one hour did not have diarrhea.

Such experiments with leucocyte extracts on typhoid infections in rabbits are sufficient for illustration, and the conclusion from them seems unavoidable that leucocyte extracts have a markedly beneficial modifying action on the course of typhoid infections or poisonings in rabbits.

The same holds true of infections in guinea-pigs treated with rabbit leucocyte extracts, but, apart from noting the fact here that subcutaneous injections, used curatively, are active in guinea-pigs, it does not seem of import to detail such experiments at this time.

Meningococcus Infection in Animals.—In meningococcus experiments rabbits suffer a marked intoxication, if not, indeed, in some instances, a true infection, when given sufficient quantities of almost any race of meningococcus intravenously. During the epidemic of cerebrospinal meningitis occurring in New York several years ago I proved this to my satisfaction many times, so that for the purpose of the following experiments I had no hesitation in selecting rabbits as the test animals.

If we analyze briefly the results of our experiments on rabbits infected with meningococcus we find the following:

In every experiment the controls died.

The total number of control animals used in the experiments, in which the treated animals received normal leucocyte or immune leucocyte extract, was nine. In one of the experiments one of the animals was greatly over weight, and should not have been used. The animal died, however, in thirteen days. Leaving this animal out of account, we have eight controls averaging 1,254 grams, with an average life of twenty hours after infection.

Of the treated animals there were thirteen. Nine of these recovered and four died, over 70 per cent. of recoveries.

The average weight of the nine animals which recovered was 1,200 grams, and of the four which died 1,062 grams, 200 grams lighter than the controls, with an average life after infection of 5.7 days.

The majority of the animals did not receive treatment until the expiration of five hours after inoculation, and a number of them not until twenty-one to twenty-four hours, some of the controls having at times died before these animals were treated with leucocyte extract. Severer tests could hardly be devised, and when the results of such tests are compared with those obtained with the use of serum they point strongly to the value of leucocyte extracts in the treatment of this infection.

Cholera and Dysentery Infections in Animals.—Experiments with cholera infections of guinea-pigs and rabbits, and with infections due to either type of the dysentery bacilli in rabbits, which always proved fatal in the control animals, have shown that these infections yield to treatment with leucocyte extract, in much the same manner as do the infections to which I have already called attention.

SUMMARY AND CONCLUSIONS FROM ANIMAL EXPERIMENTS

The character of the exact action of the extracted substance in these various infections is, of course, at present largely a matter of conjecture. The fact that treated animals, in some instances, appear more intoxicated than the untreated, may indicate an enhanced lytic action and liberation of toxic substances, thus suggesting the presence in the extracts of complementing bodies, or of digestive bodies peculiar to the leucocytes. These bodies may, of course, be present and play an active part, but the strongest impression given to one carefully following the experiments, and noting the immediate effect on temperature and the conservation and quick return to normal weight of the treated animals, is that the

principal substance at work is one active in neutralizing poisons or preventing their formation, and thus able to relieve the animal economy and give the phagocytes an opportunity to carry on their work of ingesting the micro-organisms and their non-soluble products, thus permanently rendering them harmless.

The points which to my mind at present speak most strongly for the explanation of the beneficial action of leucocyte extracts, as either poison-neutralizing or poison-prohibiting, rather than primarily bactericidal or bacteriolytic, or even one of immediate phagocytosis, are first, the effect on temperature; for, when the temperature is high it tends to be lowered, and when it is falling below normal from the intensity of the poisoning it tends to rise, on treatment; which is a sign, of course, under this condition, of returning strength on the part of an animal; and, secondly, the effect in preventing diarrhea, which is a symptom of poisoning in such intoxications. Animals treated in time rarely show diarrheal symptoms. Now, if the action of the extract were a poison-liberating one, we might possibly have a fall in temperature when it is high, following the introduction of extract, caused by a further poisoning, but we should not have a rise in temperature in an already fatally intoxicated animal; in the same way, if poison were liberated, animals receiving treatment should evince symptoms of diarrhea before the untreated ones. And, further, the experiments performed by Zinsser and myself *in vitro* and in the peritoneal cavities of guinea-pigs strongly favor a toxin-neutralizing or coagulating action, for we were able to show, in a fairly satisfactory manner, that bacterial extracts were precipitated by leucocyte extracts, and we were unable to determine any marked extracellular intraperitoneal destruction even of such sensitive organisms as cholera vibrios, or, in fact, any immediate increase in phagocytosis; and yet the animals were better off than the controls. That the action is one affecting the poisons immediately, no matter what the effect on the bacterial cells may be, seems an unavoidable conclusion, since falls of temperature of several degrees may occur within a half hour to an hour after subcutaneous administration of leucocyte extract. This fact also practically rules out an explanation of the extract as being simply a stimulator of general leucocytosis from the leucocyte-forming bases of the animal; for, even if such a leucocytosis could occur in so short a time, we know from experiment that freshly obtained living leucocytes, when introduced into an infected animal, even intraperitoneally, are practically without effect on systemic infections. The lives of the animals

are not lengthened and these intact leucocytes seem to have no influence on the temperatures.

Intravenous injections of living leucocytes have not been tried, since the results of such a procedure are of purely academic interest, being entirely outside the realm of possibility in the treatment of human infections. The use of living leucocytes in the treatment of local infections, such as those of the pleura or peritoneum, or even subdural infections, is, of course, possible, but of limited application, both theoretically and practically, and their beneficial action would probably be due to the simple regeneration of the phagocyte army, or to extracts which, unsuspectedly, accompanied the supposedly intact leucocytes introduced.

THE TREATMENT OF INFECTIONS IN MAN WITH LEUCOCYTE EXTRACT

While animal experiments are necessary, and often extremely instructive, one can, nevertheless, not argue directly from these to occurrences in man. An injection disease is not an infectious disease, and we are dealing usually with conditions in man which are at least not entirely analogous to artificial infections in animals. Artificial infections are usually accomplished by an abrupt introduction of a large quantity of infecting germs and their products; the animal powers of resistance are often immediately and severely taxed; the incubation period thus artificially shortened; and the germs themselves are not subjected to such a searching elimination, being present in large numbers, as is usually the case with the few organisms gaining a foothold by the natural channels of infection. This difference is most marked in septicemias, in which, in animal experiments, the organisms have been introduced directly into the circulation in quantities sufficient to bring about a very rapid poisoning and overwhelming of the animal, with probably only a very partial adaptation of the bacteria to the animal agents of resistance. On the other hand, the septicemic invasion in man most often follows the adaptation of the germs in some more favorable *nidus*, and probably has to do with an evolution in the bacterial resistance to the protective powers, rather than a decrease in protective strength on the part of man. Indeed, both of these processes may increase hand in hand, and we may have septicemias extending over weeks, months, and even years. We may have, in fact, an "armed peace" and the prepared bacterial army is not to be routed by the application of means which under other circumstances might prove efficacious, for we have seen how the bacteria may possibly become resistant to the protective agents of the animal body, and may continue to survive attacks which might well prove fatal to less well adapted members of their species.

Theoretically, then, I think we are safe in assuming that the infections in man which most closely simulate artificial infection in animals are fresh local infections, and infections of any character, in their earliest stages, before the bacteria have been adapted to carry on their fight with the powers of the infected body. Septicemias in man which simulate most closely those of animals are of a fulminating type, due either to a markedly virulent (already highly adapted) organism or to an unusually low state of resistance on the part of the patient.

The point which I wish, if possible, to make clear is that it seems to me that the outcome of our attempts to treat infectious diseases is, if we have the real means in our hands, probably more dependent on the degree of adaptation of the germs than the actual powers of resistance of the patient. These latter, of course, determine largely the picture of the disease, but give little information as to the power of the invader. This has been forced on me by the fact that, although we are able to cure positively acute septicemias in animals by the injection of leucocyte extract, the more subacute septicemias of man do not yield readily to our present mode of treatment, whereas even extremely severe acute and chronic localized diseases, due to the same organisms, respond to such treatment. This is true of pneumococcus, streptococcus and staphylococcus infections. I have given the matter much thought and it has seemed to me that our hope here lies possibly in a combination of heterogenous immune sera with the leucocyte extract, since it is probable that these may be able to attack different receptors, and thus destroy the organisms or prepare them for phagocytosis, whereas man's own plasma has become powerless against them. This outlook seems encouraging when we remember that organisms rendered more and more virulent for one species of animal do not always increase in virulence for another species, and may even, as is well known, become distinctly less infectious for other species.

We have evidence of this from studies of the virulence of streptococci, which, no matter what their source, even from the most rapidly spreading and fatal infections in man, may be of no particular virulence for rabbits; and, on the other hand, when rendered exquisitely virulent for rabbits, may prove practically benign when introduced in immense quantities into dogs. This is an illustration familiar to all bacteriologists and requires no more experimental evidence. We can not, however, be certain that these differences reside entirely in the plasma immunity of the animals, so that we should probably combine the leucocyte extract of the immune animal with its own serum.

The infections in man which Dr. Zinsser and I have treated, through the courtesy of various physicians, have been those due to the meningococcus, pneumococcus, streptococcus, staphylococcus, gonococcus, typhoid, colon and tubercle bacillus. Beside these bacterial infections, we have tested the influence of the treatment on cases of malaria, as the most available representative of the group of known pathogenic animal micro-organisms. In such infections it is not unlikely that the extract of the large mononuclear cells plays the major part in any beneficial effect that may be observed, as it is these cells which experiment has shown to be chiefly active in taking up cells of animal origin.

In this connection I wish to cite the history of a woman patient in St. Luke's Hospital.

CASE 1.—*History.*—Two months before her present illness this patient had been in St. Luke's Hospital suffering from malaria and had been discharged cured after treatment with quinin. She remained well for about one month, but four weeks before present admission again began to have chills, followed by high fever and sweating. These at first came every other day at about midnight, and were accompanied by the classical symptoms of malaise, headache, backache and nausea. This continued getting worse in spite of the fact that she was taking ten grains of quinin every day, and had been doing so for about six months. About three days before admission to the hospital chills began to come every day, and were now occurring during the late afternoon. On admission to the hospital, on Oct. 27, 1908, a chill occurred between four and five in the afternoon, her temperature reaching 104. The chill lasted thirty minutes. During the night the temperature began to fall again, and by noon on the following day had reached 97 F. It did not remain low for more than an hour, and between 2 and 4 o'clock another chill occurred, the temperature rising abruptly to 106.2 F. A blood examination made at this time showed 7,300 leucocytes, 60 per cent polynuclears, and numerous tertian parasites present. Immediately after this second chill it was decided to attempt treatment with leucocyte extract, no quinin having been administered since the admission of the patient to the hospital.

Treatment With Leucocyte Extract.—Ten c.c. of extract were injected subcutaneously, at about 9 p.m., about five hours after the highest temperature reached during the chill. The temperature during the night fell as usual, reaching 98 F. the following morning, when another 10 c.c. of extract were injected. A third dose was given at noon. On this day no chill occurred, the highest temperature reached being 100.8 about 6 p. m. No more leucocyte extract was given that day, but on the following day 10 c.c. were given about 9 a. m. The temperature on this day reached 102.2, but no chill occurred. Concomitant with the omission of the chills there was a very marked improvement in the general condition of the patient. Almost immediately after the first injection a reduction of the nausea, the malaise, and restlessness occurred, with complete alleviation of the headache, which had been extremely troublesome. Numerous blood examinations during this time showed, however, that there was absolutely no diminution of, or change in the development of, the plasmodia. During October 31 and November 1 no extract was given. No chills occurred, but each day the afternoon temperature exceeded that of the preceding day, on November 1 reaching 104 F. at 8 p. m. On November 2, at about noon, 10 c.c. of leucocyte extract were given, and on this day the temperature did not exceed 100.4. On November 3, 10 c.c. were given shortly after noon, and the temperature did not exceed 103, the pa-

tient feeling extremely well. On November 4, the following day, no further leucocyte extract was given, nevertheless, the temperature did not exceed 100.8, and the patient felt so well that she was allowed up in a chair. No further injections of extract were made, and on November 5 and 6 the afternoon temperature became gradually higher, reaching 103 at 6 p. m., and on November 7 a sharp afternoon rise to 104.2 was accompanied by a chill. This chill on November 7 was the first true malarial chill which had occurred since the beginning of treatment on October 28. During all this time the patient had been feeling extremely well and all the symptoms, which were analogous to those of toxemia in malaria, had been alleviated. On the other hand, absolutely no diminution or change in the plasmodia was noted. On November 8, 5 grains of quinin were given every four hours, which, after a few days, resulted in complete cure and disappearance of the plasmodia from the circulating blood.

Although isolated, this case showed such a striking reaction to the first administration of leucocyte extract and such an unquestionable return of symptoms upon omission of the leucocyte extract that, while, of course, a single case warrants no conclusions, the evidence certainly favors the opinion that the extract had a distinct neutralizing value for the poisons elaborated by the plasmodia. It is interesting, moreover, to note that the symptoms of the disease were entirely alleviated without there being any visible effect on the plasmodia, a fact which seems to indicate that certain phenomena appearing during this disease may be interpreted as the results of toxemia.

That malaria can be thus influenced would seem to be a fact of more than passing interest, and it is mentioned here as it holds out the possibility of the favorable outcome of the application of such measures to the treatment of the spirochætal and trypanosomal diseases and other infections of protozoan origin in man.

There is not time, nor is this the place, to go into the histories of the individual cases, except by way of illustration of the various bacterial diseases which we have treated. In connection with Dr. Zinsser I have lately published the results obtained in the treatment of a number of meningitis patients, and in a small number of patients suffering from lobar pneumonia and pneumococcus infections, and to these articles I must refer any one interested for details.[2]

Meningococcus Cases.—It may be of interest to state, however, that fifteen of the meningitis patients treated by us were under fifteen years of age; of these, three died, leaving 80 per cent. of recoveries with no sequelæ. Of the patients over fifteen years, there were seven, five of whom died. This result may have been due to the fact that several of these adult patients were *in extremis* when admitted to the hospital. In spite of this, under treatment some of the patients showed a marked im-

2. Jour. Med. Research, 1908, xiv.

provement and did not die before twenty-seven, seven, thirty-eight, eleven, and twenty-five days after treatment was begun. Of the children who were treated, but who died, one survived seventy-nine days, one sixty-two days, and one, a baby of seven months, twelve days, after treatment was instituted.

It seems also of interest to note the fact that in seven cases in which treatment was begun *subsequent* to the seventh day of the disease there was 100 per cent. of recoveries without sequelæ. Treatment was not begun in these cases until the elapse of seventeen, twenty, forty-seven, forty-one, fifty-three, thirty-nine, and eighty-two days after the first symptoms developed, and a reference to the histories would show that these patients were, as a rule, in grave condition.

Almost without exception there was an improvement in those symptoms which, in this disease, depend largely on the central nervous system. Vomiting, delirium, stupor and hyperesthesia were usually diminished or entirely allayed after one or two administrations of quantities ranging from 5 to 20 c.c.

Marked reduction in the temperature following injections was noticeable in many of the cases. In some of these cases, however, the diminution of the fever was a temporary phenomenon, limited to the twenty-four or forty-eight hours immediately following the injection, a fact which also argues strongly for the idea of poison neutralization.

The actual percentage of recoveries among these patients was about 64 per cent. If 70 to 75 per cent. be accepted as the usual death rate, and the basis for determining the value of the serum treatment of meningitis, then the fact that 64 per cent. of our patients recovered would seem to indicate some curative value in the extract. And if this is true, it also indicates that if the antimeningitis serums are really toxin-neutralizing, or contain the same antibodies as the leucocyte extract, then these sera should be efficacious when administered subcutaneously, which is not the fact. I am inclined to believe that a combination of these treatments, immune serum given subdurally and leucocyte extract subcutaneously, might lead to more favorable results than the use of either separately.

Pneumococcus Infections.—In considering the effect of leucocyte extract on the course of uncomplicated lobar pneumonia it is impossible, in view of the small number of cases, to arrive at a definite opinion. Not more than twelve or fifteen patients have been systematically treated, and of these one has died. This might be true of any series of the same number. However, the uniformity with which temperature changes and the relief of toxic symptoms follow the administration of moderate

amounts of extract in the lighter cases, and often in the severe cases after the administration of larger or repeated doses, points to a toxin-controlling and beneficial action of the extract. One case which has lately come under the observation of Dr. Patterson may serve as an illustration.

CASE 2.—Reported by Dr. Patterson. Mrs. G., 78 years old, had emphysema and chronic bronchitis with asthma; developed acute bronchitis.

January 4: Temperature 101.3. Diagnosis of probable pneumonia.

January 5: Very sick; evidences of toxemia (character of pulse, cyanosis of finger nails and lips, prostration) most marked. Looked as though patient would surely die. Seen by Dr. S. W. Lambert: Pneumonia; patient will probably die.

January 6: Patient about as yesterday, but condition not quite so toxic. At 3 p. m. patient cyanosed, appeared very sick, but not so much so as yesterday. Leucocytes, 10,900; polynuclears, 78 per cent. Twenty c.c. of leucocyte extract injected.

January 7: Distinct improvement in toxic symptoms; patient had developed appetite and asked for egg and toast. At 5:10 p. m., P. ex. Over left upper lobe in front, marked dulness; feeble breathing; but no change in quality of the voice and breathing. "Since first injection there is marked improvement in the patient's appearance and general condition, and a marked improvement in the character of the pulse." Leucocytes, 9,200; polynuclears, 86 per cent. Twenty c.c. of leucocyte extract injected.

January 8: "Patient decidedly better." Dulness over left upper lobe less marked. Pulse of a better quality. At 3 p. m. 20 c.c. of leucocyte extract injected. Leucocytes, 9,200; polynuclears, 90 per cent.

January 9: Patient's condition highly satisfactory. Twenty c.c. of leucocyte extract given. Course uneventful thereafter.

As an illustration of the effect on a patient in the very early stage, and possibly suffering from a less severe infection, the following is interesting:

CASE 3.—*Patient.*—Mohan, male, adult, admitted to St. Luke's Hospital, service of Dr. T. C. Janeway. Family and previous history irrelevant.

Present Illness.—Four hours before admission, while at work, the patient had a shaking chill. His teeth chattered, his lips were blue, and he felt feverish. At the same time he began to suffer from pain in the lower anterior part of the right chest which was markedly aggravated by deep breathing.

May 10, 1907: Admitted to St. Luke's Hospital in late afternoon. Temperature, 102; pulse, 100; respiration, 26. Over the lower lobe of the right lung there were typical signs of consolidation. The sputum was blood-streaked. The leucocytes were 26,000; polynuclears, 89 per cent.

May 11: The condition of the patient was unchanged; temperature rose, reaching 104 at noon. Leucocyte extract, 6 c.c., subcutaneously injected. Following this injection there was a sharp and steady drop in the temperature, reaching 98.8 on the morning of the following day.

May 12: During the morning of this day temperature steadily rose, reaching 103 F. at noon. Leucocyte extract, 10 c.c., injected in early afternoon. Temperature again dropped, reaching 98 at midnight.

May 13: The general condition of the patient was very much improved, breathing was easier, pulse and respiration had become normal.

After a rapid convalescence patient discharged cured.

First injection was given on second day of diseases. Total quantity given, 16 c.c.

This case is interesting primarily because of the apparently sharp and rapid response of the temperature to the injections of the leucocyte extract. The occurrence of the crisis on the third day of the disease is a phenomenon sufficiently rare to encourage the opinion that it may have been at least in part due to the injection.

Such occurrences as these, backed by the conclusive evidence of the animal experiments, would certainly seem to warrant an extended and careful study of the influence of this agent on pneumococcus infections in man and make us hopeful that many an otherwise fatal illness may become comparatively benign under its influence. This hope is strengthened by evidence gathered from the study of infections due to the streptococcus, so closely related to the pneumococcus in many ways.

Streptococcus Infections. Erysipelas.—Dr. Adrian Lambert in his wards at Bellevue Hospital, during last July and this January, has treated about fifty cases of erysipelas by this method. Erysipelas is the ideal infection to study, for the chief lesion is in plain view, and, besides, there is a marked temperature reaction to the infection. In adults the disease is not very fatal, but in children under one year of age the mortality is, I understand, very high. While the history of these cases will shortly be published in detail, Dr. Lambert has kindly drawn his conclusions for me. They are as follows:

Leucocyte extract will abort infections which are treated within the first forty-eight hours.

It will ameliorate the course of older infections and may abruptly terminate them; the longer the infection has existed, the less likely is the latter to take place, but it tends to shorten the course of the disease.

The toxic symptoms, delirium, headache, nausea and vomiting, are modified and relieved; local pain is lessened.

The rash does not disappear immediately, but is apt to be localized.

The spreading intractable lesions of the back and body are apparently affected as readily as those occurring on the face and head.

Pus formation is aborted, and sequelæ are rare, if they occur at all.

About 50 per cent. of babies under one year of age have recovered from the erysipelas.

The effect of leucocyte extract on erysipelas strongly suggests its use in the streptococcus infections complicating the exanthemata, and, of course, in streptococcus infections in general. Many of the dangerous sequelæ of these diseases might be avoided by its use.

Staphylococcus Infections. Local acute and chronic staphylococcus infections respond almost immediately to treatment with the extract, and furunculosis of intractable type is halted and apparently cured. Dr. Zinsser has treated eleven patients who had staphylococcus infection. In these, after treatment was begun, surgical interference was always un-

necessary. The following history illustrates the response of chronic furunculosis to the treatment.

CASE 4.—G. P., assistant carpenter, St. Luke's Hospital, 22 years old, Swede, athlete, general health excellent, for three years had been troubled with persistent pimples on the face. For the four months preceding examination he had had boils on the neck and behind the ears, a new one developing every other day. For the last few weeks boils had appeared on both legs and in the left axilla. For the last two weeks the patient had never gone two days without the development of a new furuncle. These had been growing steadily more severe, and during the last week he had developed a very painful furuncle with extensive induration within the external meatus of the right ear. On examination he was found to have at least fifteen to twenty boils on the back of the neck and behind the ears. *Staphylococcus pyogenes aureus* was cultivated from the boils.

October 7: Ten c.c. of leucocyte extract injected.

October 8: No new boils appearing and old ones improved.

October 10: Ten c.c. leucocyte extract injected. No new boils appear.

October 11: Ten c.c. given prophylactically.

No new development of furuncles until November 28, when a small pimple appeared on the back of the neck, which was quite angry and painful, and 10 c.c. of leucocyte extract was injected.

December 1: No new boils had developed. The patient appeared entirely well, and has so remained till the present time.

As an illustration of the effect of leucocyte extract on an acute and severe infection, not well adapted to surgical interference, the following case may be cited:

CASE 5.—Three weeks before present illness the patient, a woman, developed an acute dacryocystitis. There were several attacks of this condition following the introduction of a probe. There appeared to be a stricture in the nasal duct. *Staphylococcus pyogenes aureus* was at this time isolated from the inflamed area in the lachrymal duct and from the nose. Following an attempt to correct the stricture on Jan. 12, 1909, infection from the nose traveled up through the nasal duct into the orbit. The patient's temperature rose to 103.4 F. and a rapidly spreading acute inflammation developed in the orbit, from the pus of which *Staphylococcus pyogenes aureus* was recovered in pure culture. There was marked exophthalmos, complete immobility and protrusion of the eyeball. It was the opinion of the attending physician that the tissues behind the eye were edematous and that the orbit probably contained pus.

January 13: Ten c.c. of leucocyte extract injected. Temperature dropped to 100.2 on the folowing day, but rose again to 101.8 in afternoon. On January 14, two injections of 10 c.c. of leucocyte extract.

January 15: Temperature dropped to 99.8: Marked improvement in general condition and in .ocal lesion. During the night of January 15, temperature again rose to 100.8, but dropped on January 16 to 99. Ten c.c. of leucocyte extract injected. Temperature did not go above 100.2, on following morning being 99.4. General improvement progressed, and there was marked clearing up of local lesions. Rapid and uneventful convalescence.

Time will not permit me to call attention to work in other infections. Indeed, in the case of most of these the data are too scanty to warrant the expression of any definite opinions.

In conclusion, then, let me say that no one realizes more fully than I the vast amount of work, experimental and clinical, which must be done before the value of the work presented to you can be fully determined and the crude weapons, new to our hands, be better fashioned and more skilfully handled.

437 West Fifty-ninth Street.

THE CLOT CULTURE IN CONJUNCTION WITH THE AGGLUTINATION TEST IN TYPHOID*

RANDOLPH LYONS, M.D.
NEW ORLEANS

During the past few years great advances have been made in the early diagnosis of typhoid fever by the isolation of the bacillus through improved blood-culture methods. Though these methods facilitate the recovery of the bacillus, a well-equipped laboratory and a knowledge of bacteriologic technic are essential; therefore, in country districts, where there is no available laboratory, the practitioner is obliged to depend upon the agglutination test as an aid in diagnosis.

As a diagnostic measure, the agglutination test is now generally conceded to be unreliable, especially in the early days of the disease, being only occasionally positive before the end of the first week and not reaching its maximum until the third and fourth weeks. Thus out of 42 cases at the Charity Hospital of suspected typhoid, from which a specific organism was isolated, but 53.3 per cent. gave a positive Widal on admission, though the percentage of positive blood cultures was 85.7 per cent. It must be mentioned, however, that 3 of the cases were paratyphoid infections, which necessarily explains some of the negative typhoid agglutination tests. It is hardly fair to state on so small a series of cases that the percentage of paratyphoid infections in New Orleans averages as high as 7.1 per cent. Four per cent., however, may be taken as a conservative estimate. In view of this it would seem that we might expect at least 4 per cent. of our Widal reactions to be negative, unless agglutination tests were performed with paratyphoid strains of both groups (A and B). Here, again, we meet with the same objection as arises with the Widal test; namely, that paratyphoids are seldom positive in the early days of the disease.

The laboratory method *par excellence* for the early diagnosis of typhoid fever is the blood culture. Now, might it not be of the greatest importance, when blood is sent into a laboratory for the Widal test and found negative, to make cultures from this material with a view of isolating the typhoid bacillus?

Fornet[1] and others have shown that the typhoid bacillus could be isolated from clotted blood. His clot culture method, however, is rarely

*From the Laboratory of Clinical Medicine, Medical Department of Tulane University.

1. Fornet: Ein Beitrag zur Züchtung von Typhusbacillen aus dem Blut. München. med. Wchnschr., 1906, liii, 1053.

mentioned and seldom, as far as I have been able to ascertain, used in this country. This method has, in my limited experience with it, proved extremely valuable in combination with the Widal test.

Müller and Gräf[2] in 1906 obtained the *Bacillus typhosus* from the blood in 110 out of 360 cases. During this same year Fornet isolated the bacillus in 14 out of 19 typhoid cases. In 1907 Kurpjuweit, employing Müller and Gräf's method, obtained positive results in but 12 out of 100 cases. All these investigators used the blood clot from the Widal tubes which had been sent into their laboratories for the agglutination reaction.

It is, of course, essential for the performance of clot cultures that the blood be sent in Widal pipettes, and not in the dried state. It occasionally happens that a physician may have no Widal pipette with him nor any glass tubing convenient to make one and is thus unable to collect the patient's blood. I have devised a simple means of making a Widal tube, which, under such circumstances, will be found extremely useful: An ordinary hypodermic tablet vial is heated at one end over a flame (an alcohol lamp serves the purpose excellently) and, when soft, the end is drawn out into a capillary tube with forceps. The capillary extremity, after cooling, is then held and the same procedure repeated for the other end of the vial. Such a pipette, when filled with blood, may be sent any distance with impunity, provided both capillary ends are thoroughly sealed over the flame.

In a paper[4] read before the New Orleans Parish Medical Society in January, 1909, I reported four positive results out of six typhoid cases with Fornet's method and thought that the method might prove of distinct value in conjunction with the Widal test. Fornet's method was chosen in preference to that of Müller and Gräf because it is simple and offers many advantages over the latter. Müller and Gräf used the serum from the Widal tubes sent into their laboratory for the agglutination test, then removed the clot, which remained in the tubes, and rubbed it over the surface of Conradi Drigalski plates. Fornet, on the other hand, planted the clot in bile.

There are many objections to the plate method as used by Müller and Gräf: 1. The bacilli may not be released from the specific agglutinins as in the case where the bile medium is employed. 2. As the clot

2. Müller and Gräf: Nachweis von Typhusbakterien in eingesandten Blutproben. München. med. Wchnschr., 1906, liii, 69.

3. Kurpjuweit, O.: Ueber den Nachweis von Typhusbacillen in Blutgerinnseln. Arb. a. d. k. Gsndhtsamte, 1907, xxv, 229.

4. Lyons: Comparative study of the blood culture and agglutination test in typhoid. New Orleans Med. and Surg. Jour., April, 1909, xli.

is simply rubbed over the medium, there is only a chance for the bacilli on the external surface of the coagulum to be transplanted, whereas in the bile culture the clot is dissolved. 3. Many of the bacilli transferred to the plates may not grow; therefore, unless they are numerous, the method leads to an erroneous result. 4. The typhoid colonies[5] in the plate method, if few, may be overlooked or overgrown by saprophytes. In Fornet's method the clot from the Widal tube, after the serum has been removed for the agglutination test, is planted in 5 c.c. of sterilized ox-bile and the mixture incubated at 37 C. A transfer to agar slants or blood serum may be made after twelve hours. The occurrence of contaminations is, fortunately, rare, but, should they occur, a pure culture may be procured by plating or by a method I have employed of taking a loopful of the water of condensation from the contaminated agar slant and inoculating a fresh bile tube. After incubating again a pure culture will usually be obtained.

The tests were made with a view to estimating their combined value as a diagnostic measure and were performed in the following manner: On all suspicious febrile cases admitted to Prof. George Dock's wards a Widal was made and the clot planted in 5 c.c. of sterilized ox-gall; as a control a blood culture was taken at the same time. The total number of cases examined was 20; two of them were paratyphoid infections:

TABLE I.—WIDAL REACTION, BLOOD AND CLOT CULTURE IN TWENTY CASES

	Case.	Week.	Widal Reaction.	Clot Culture.	Blood Culture.
	1	2nd	—	+	+
	2	4th	+	+	+
	3	3rd	+	+	+
	4	2nd	+	+	+
	5	3rd	—	—	+
(Paratyphoid)	6	2nd	—	+	—
(Paratyphoid).	7	1st	—	+	—
	8	2nd	—	—	—
	9	1st	—	—	—
	10	2nd	+	—	—
	11	3rd	+	—	—
	12	3rd	+	—	—
	13	3rd	+	—	—
	14	3rd	+	—	—
	15	3rd	—	+	+
	16	2nd	—	—	+
	17	2nd	—	—	+
	18	1st	—	+	+
	19	2nd	+	+	+
	20	3rd	+	+	+
Total.....	20		10 (60%) pos.	12 (60%) pos.	18 (90%) pos.

5. Peabody, Francis W.: The bacteriologic diagnosis of typhoid fever. Jour. Am. Med. Assn., 1908, li, 979.

From Table I it will be noted that in only 5 of the cases were the Widal reaction and clot culture positive at the same time. In Case 6 a positive paratyphoid agglutination test was not obtained until twelve days later, though the blood was tested a number of times against various strains. Case 7 gave a positive paratyphoid agglutination test ten days after its isolation from the clot. Both paratyphoids were isolated from the blood-clot. But three of these cases failed to give a diagnosis with both tests.

TABLE II.—COMPARATIVE VALUE OF THE WIDAL AND CLOT-CULTURE METHODS

No. of Cases.	Week.	Widal Positive.		Clot Culture Positive.		Blood Culture Positive.	
		No.	%	No.	%	No.	%
3	1st	0		3	100	3	100
8	2nd	3	37.5	5	62.5	8	100
8	3rd	6	75	3	37.5	6	75
1	4th and on	1	100	1	100	1	100
—		—	—	—	—	—	—
20		10	50	9	60	18	90

An analysis of Table 2 shows that only 50 per cent. of the Widal reactions and but 60 per cent. of the clot cultures were positive; if the results of the two, as shown by Table 1, are combined, however, the percentage of positive results is raised to 85, which almost equals the percentage of positive blood cultures. It is a striking fact that the clot culture is most often positive early in the disease, while just the opposite is true of the Widal test; hence the probability of making a diagnosis at any stage of the disease is greatly enhanced by the combination of the two methods.

CONCLUSIONS

1. Practitioners should be encouraged when sending blood to a laboratory for the Widal test to send it in the fluid state.[6]

2. In conjunction with the agglutination test the clot should be removed from the Widal tube and cultured in bile, even though the Widal reaction be positive, for the recovery of the organism is final, while a Widal may exceptionally be positive in other conditions.[7]

---

6. Attention should be called to the fact that, according to Section 495, Postal Laws and Regulations, liquid cultures, or cultures of micro-organisms in media that are fluid at ordinary temperatures, can not be sent through the United States mails, and that pathologic specimens in the solid state may be mailed only to United States, state or municipal laboratories. The postoffice rules were published in the Journal of the American Medical Association, 1909, lii, 791.

7. Backer, Wilhelm, and Ruhland, George C.: Typhoid agglutination reaction in a case of epidemic cerebrospinal meningitis. Jour. Am. Med. Assn., 1909, lii, 13.

3. By combining the above two methods the chances of an early diagnosis are almost doubled.

4. By the clot-culture method cases of paratyphoid infection may be early recognized, which is an important factor in prognosis.

5. Fornet's method has many of the advantages of the method of Müller and Gräf, with none of the objections to the latter.

2344 St. Charles Avenue.

A MODIFICATION OF THE SAHLI BUTYROMETRIC TEST MEAL

J. C. FRIEDMAN, M.D.
CHICAGO

The need of some improvement in our methods of determining the gastric functions is evident when we consider the limitations of the present methods. For instance, if after the administration of an ordinary test breakfast we aspirate an excessively large amount of contents, it is impossible to say whether the excess is due to abnormal secretion of gastric juice, to impaired motility, or to both. If, however, we should introduce with the test meal a certain amount of some substance which was not affected by gastric ferments, or absorbed by the stomach, something which would mix thoroughly with the gastric juice, then by estimating the amount left at the end of a given period we could determine how much of the test meal had passed on into the intestine; i. e., the gastric motility, and how much of the aspirated contents consisted of test meal, how much of the gastric juice.

Sahli[1] proposed the following meal, based on such considerations: An emulsion of fat is prepared by roasting 45 grams of flour, thoroughly mixed with 15 grams of butter; 350 c.c. of water are added and the whole boiled two minutes. This process makes rather an agreeable thick soup. Of this 300 c.c. are given the patient and 50 c.c. retained for a fat determination. After one hour the stomach contents are aspirated as completely as possible. As it is not possible to aspirate the total contents, the residue is calculated according to the method of Matthieu,[2] viz.: A definite amount of water—say 300 c.c.—is poured down the stomach-tube, thoroughly mixed with the remaining stomach contents, and the whole again aspirated. Then both diluted and undiluted contents are titrated and the residue calculated by the following equation: Let x = residue, a = acidity of undiluted contents, and b = acidity of residue diluted with 300 c.c. water. Then:

$$\times = \frac{300 \times b}{a - b}$$

Adding this amount to the quantity originally aspirated, we have *TO*, or the total stomach contents at the time of aspiration.

1. Sahli: Klinische Untersuchungs Methoden, 1902, p. 412.
2. Matthieu: Arch. f. Verdauungskr., 1896, i, 348.

Two fat determinations are then made to ascertain how much fat the test meal contained and how much remained in the stomach at the time of aspiration. Sahli uses Gerber's acido-butyrometer, employed in dairies in Switzerland, in which the emulsion of fat is broken up by strong sulphuric acid and amyl alcohol, centrifugalized, and the fat per cent. read off in the necks of bottles empirically graduated. If we give a patient 9 grams of fat contained in 300 c.c. of soup and find only 3 grams left in the stomach after one hour, then this would correspond to 100 c.c. of soup, and if we aspirated 200 c.c. of stomach contents and 100 c.c. of it is test meal then the other 100 c.c. must be gastric juice. Algebraically expressed:

Let TO = total amount of stomach contents and F = per cent. of fat in original soup. Let f = per cent. of fat in aspirated contents. Let TM = test meal and GJ = gastric juice. Then TM or the amount of the test meal contained in aspirated contents $= \frac{f \times TO}{F}$ and of course GJ or the gastric juice $= TO - TM$.

We now know what part of the stomach contents is test meal and what part is gastric juice. The relation of these two to each other we call the secretory quotient or Q.

Furthermore, in an ordinary test meal what we titrate is the acidity, not of the undiluted gastric juice, but of gastric juice diluted by more or less of the fluid contained in the given test meal. If, however, we know the acidity of the mixture and how much of the mixture is gastric juice, it is easy to calculate that by the following equation:

Let a = acidity of the aspirated stomach contents (determined by usual titration) and A = calculated acidity of the undiluted gastric juice and TO = total amount in stomach at the time of aspiration and GJ = amount of gastric juice in the contents, then:

$$\frac{A = a \times TO}{GJ}$$

The motility in this method is represented by the relation of the amount of test meal which has left the stomach to the total amount given, or:

$$\frac{M = 300 - TM}{300}$$

As will be seen, the only extra work involved is the preparation of the test meal and two fat determinations, the calculations, of course, being very simple. Objections to the method soon appeared, however. It was asserted that the preparation of the meal was difficult, that the presence of such a large amount of fat in a meal inhibited gastric secre-

tion, and, most essential, that the emulsion was not stable and did not mix evenly with the gastric juice. This last objection, if true, nullifies the whole procedure, which is based on the theory that the fat remains evenly diffused throughout the whole stomach contents. To take the instance given above, we supposed a soup containing 3 grams of fat to the 100 c.c. If in the stomach the fat should rise to the top and remain behind while the fluid passes through the pylorus, it will be seen that our only means of deciding how much of the original test meal is left in the stomach is gone.

After working some time with this meal it was found that these objections were justified, and a search was made for a simpler and more stable emulsion. After many fruitless attempts at artificial ones, a satisfactory substance was found in condensed milk. If we dilute condensed milk two or three times, add some gastric juice and keep the test-tube ever so slightly in motion, it will be found that the flocculi resulting from the coagulation are exceedingly fine, uniform in size and microscopically the fat globules almost as fine as in fresh milk and almost as evenly divided.

Of the different brands tested, that known as "Carnation" proved the most satisfactory and was used in the following work.

TABLE 1.—RESULTS IN NORMAL INDIVIDUALS

Case Number.	Total Amount in Stomach=*TO.*	Ratio of Fat in Meal to Fat in Stomach Contents=*F:f.*	Calculated Amount of Test Meal in Aspirated Contents=*T. M.*	Calculated Amount of Gastric Juice in Aspirated Contents=*G. J.*	Secretory Quotient.	Motility.	Titrated Acidity.	Calculated Acidity of Pure Gastric Juice.	Diagnosis.	Remarks.
1	282	2.2:1.3	166	116	0.7	0.61	54	131	Normal.	
1	287	2.9:1.5	150	137	0.91	0.5	62	130	Normal.	
1	258	2.0:1.1	142	116	0.82	0.52	68	151	Normal.	
1	200	1.9:1.0	105	95	0.9	0.65	74	155	Normal.	
1	238	3.0:1.7	135	103	0.76	0.53	56	129	Normal.	
2	134	2.8:1.8	76	58	0.7	0.7	58	134	Neurasthenia.	Only 250 c.c. of meal were given.
3	85	2.0:1.0	42.5	42.5	1.0	0. 6	50	100	Neurasthenia.	

For making the fat determinations the Babcock method was employed, a small hand centrifuge being used, such as is sold for the determination of butter fat in milk and cream for dairy purposes. The following is the routine: 120 c.c. of condensed milk are diluted with

water to make 350 c.c., 50 c.c. retained for a fat determination and 300 c.c. given the patient. In fifty minutes the contents are aspirated as completely as possible, 200 c.c. water poured down the tube, thoroughly mixed with the residue and again aspirated. A titration of the stomach contents, another of the diluted residue, a fat determination of the original meal, and one of the aspirated contents are all that are necessary for the final calculation. Blood, lactic acid, etc., are tested for as usual. The accompanying tables give results obtained by this method.

In normal individuals, then, the total amount in the stomach after fifty minutes varies considerably, viz.: from 85 c.c. to almost 300, depending, of course, on normal individual variations. Second, the relation between the amount of milk and the amount of gastric juice, which we call the secretory quotient, varies normally between 0.7 and 1 even in the same individual at different times, while between different individuals the variation is no greater. Third, the motility, or the relation between the amount of milk that has passed the pylorus to the amount given, varies between 0.5 and 0.86. If a less amount passes the pylorus we have hypomotility; if a greater amount, hypermotility. Fourth, the figures for titrated acidity are, of course, those known from the Ewald test breakfast and varied between 40 and 76, a variation from the mean of 31 per cent. The calculated acidity, however, was very much more constant, lying between 120 and 150 (occasionally a little lower), a variation of only 10 per cent. In other words, the acidity of the gastric juice as it is poured out by the glands is remarkably constant, much more so than the figures which we obtain from titrating a test meal would indicate. This fact, which was first demonstrated by Pawlow on dogs, was later verified by Bickel[3] in two patients with gastric fistulas. He found that the acidity was constantly between 110 and 140, only the first part secreted having a lower acidity, due to neutralization by the gastric mucus. Bickel also verified the results of Pawlow in regard to the quantity and found that it varied considerably according to the kind of food, condition of patient, etc. By the present method, of course, we do not estimate the total amount secreted during the whole digestive act, but simply the amount in the stomach at the time of aspiration. This, we have found, normally bears a constant relation to the amount of test meal in the stomach at that time, as indicated by the secretory quotient; or:

$$\frac{GJ}{TM} = 0.7 \text{ to } 1$$

3. Bickel: Deutsch. med. Wchnschr., 1906, xxxii, 323; 1907, xxxiii, 1201.

When the two do not bear this relation, the condition is pathologic; if the relation of gastric juice to test meal is greater than 1 we have hypersecretion; if less than 0.7, we have hyposecretion. Of course, if we remove the test meal earlier, we find a condition of hyposecretion; i. e., a lower proportion of gastric juice. For instance, removing test meal in thirty minutes, 321 c.c. remained in the stomach; of this quantity, only 85 c.c. were gastric juice, the remainder being test meal, a secretory quotient of 0.36. This was, of course, normal for a thirty-minute period, but would have been pathologic for a fifty-minute period. So much for the normal figures. There are theoretically six possible variations. There may be hypersecretion, or hyposecretion, hypermotility or hypomotility, hyperacidity or hypoacidity, or combinations of these.

The following table illustrates the findings in some typical cases of so-called hyperacidity:

TABLE 2.—HYPERSECRETION

Normal secretory quotient (Q) varies between 0.75 and 1. Hypersecretion is present when Q is more than 1.

Case Number.	Total Amount in Stomach = $T.$	Ratio of Fat in Meal to Fat in Stomach Contents = $F./f.$	Calculated Amount of Test Meal in Aspirated contents = $T.M.$	Calculated Amount of Gastric Juice in Aspirated Contents = $G.J.$	Secretory Quotient = $Q.$	Motility.	Titrated Acidity.	Calculated Acidity of Pure Gastric Juice.	Diagnosis.	Remarks.
4	156	3.0:1.3	68	88	1.3	0.77	72	128	Neurasthenia.	Test meal consisted of 125 c.c. each of condensed milk and water.
5	195	2.8:1.0	70	125	1.8	0.72	64	100	Neurasthenia.	Test meal consisted of 125 c.c. each of condensed milk and water.
6	474	2.8:9.0	152	322	2.1	0.39	82	121	Benign pyloric stenosis.	Test meal consisted of 125 c.c. each of condensed milk and water.
6	296	2.8:9.0	95	201	2.1	0.6	66	97	Benign pyloric stenosis.	Test meal consisted of 125 c.c. each of condensed milk and water.
7	672	2.1:0.6	224	448	2.0	0.25	68	103	Benign pyloric stenosis.	Test meal consisted of 125 c.c. each of condensed milk and water.

Case 6 was a benign stenosis of the pylorus of ten years' duration. The stomach was thoroughly emptied before the test meal was given (and with some practice this can be done so that at the utmost only 25 to 30 c.c. are left). Fifty minutes later the amount removed was 496 c.c. Ordinarily we would have no certain means of knowing whether this excessive amount was due to impaired motility or hypersecretion of gastric juice, as either would produce this result. We find on analysis

here, however, that, while the motility is somewhat impaired, yet the major portion of the excess is due to hypersecretion, there being 2:1 times the normal proportion present. In the first test the motility was markedly impaired, viz.: 0.39. In the second, after two weeks of gastric lavage, motility had improved somewhat, but did not remain permanently so till after a gastroenterostomy had been done. The titrated acidity in one estimate was 82, showing an apparent hyperacidity, but the calculated acidity of the pure gastric juice was 121, well within the normal limits. The functional diagnosis reads, then, hypersecretion and impaired motility, the characteristic findings of benign stenosis.

In Case 4 the total amount in the stomach was 156 c.c., but the relation of gastric juice to test meal in that was higher than normal, viz.: 1.3, instead of 1, a hypersecretion, in other words. The titrated acidity was 72, slightly above normal, but the calculated acidity was only 128. Therefore, the stomach was pouring out a larger amount of secretion than normal, but with normal acidity. Motility was normal.

Diagnosis: Simple hypersecretion with good motility, a neurosis, as the course showed.

To illustrate the value of this method in distinguishing between hypersecretion and impaired motility, we may compare Tables 2 and 3.

TABLE 3.—HYPOMOTILITY

Normal motility varies between 0.5 and 0.8. Hypomotility is present when less than 0.5 of meal passes pylorus.

Case Number.	Total Amount in Stomach=*T.O.*	Ratio of Fat in Meal to Fat in Stomach Contents=*F.:f.*	Calculated Amount of Test Meal in Aspirated Contents=*T. M.*	Calculated Amount of Gastric Juice in Aspirated Contents=*G. J.*	Secretory Quotient =*Q.*	*Motility.*	Titrated Acidity.	Calculated Acidity of Undiluted Gastric Juice.	Diagnosis.
27	436	2.9:1.4	210	226	1.08	0.16	58	112	Atony.
27	340	2.7:1.3	164	176	1.07	0.34	62	112	Atony.
27	350	2.7:1.3	150	160	1.07	0.4	60	116	Atony.
28	258	2.5:1.4	144	114	0.78	0.42	56	126	Stone in common duct.
28	386	2.6:1.1	160	228	1.4	0.26	60	146	Stone in common duct.
29	305	1.9:1.1	177	128	0.72	0.4	34	82	Atrophic cirrhosis of liver.
30	441	3.0:1.6	235	206	0.88	0.22	70	149	Benign pyloric obstruction.

The cases in Table 3 all show impaired motility of the first degree only; that is, the stomach emptied itself over night. In Case 27, for

instance, all three tests gave large amounts of stomach contents—from 370 to 436 c.c., much beyond the normal. The same question arises as to whether this is due to impaired motility or hypersecretion. The results show, however, that the aspirated contents consisted of about equal parts of gastric juice and test meal; that is, the secretory quotient was about 1; and, therefore, that the increased contents must be due to impaired motility, and this the figures show, the motility varying from 0.16 to 0.4, considerably below normal. The same points are illustrated by Cases 28, 29 and 30, in all of which impaired motility without hypersecretion is found. As far as the reliability of this meal as a test of motor function is concerned, I may say that in all cases in which the Riegel motor meal showed impaired motility this method indicated it also, and in some cases of apparent slight impairment, as in simple atony, it proved positive where the Riegel meal was negative, so that it is, if anything, a more delicate indicator of motility.

Cases of impaired motility complicated by secretory changes are tabulated under the latter headings.

The third possible pathologic variation is hyperacidity, a name until recently used to indicate all of those conditions in which the titrated acidity was above a certain maximum, about 70. Rubow,[4] from theoretical considerations alone, concluded there was no such condition possible, all the cases of so-called hyperacidity being due simply to hypersecretion of juice of normal acidity. If the normal stomach contents one hour after a test meal consist of equal parts of test meal and a gastric juice of normal acidity (say 120), then the mixture would have an acidity of 60, and the titration would give us the latter or normal figures. If, however, the stomach contents contained one-quarter test meal and three-quarters gastric juice of the same acidity (120), then the mixture would have an acidity of 90 on titration, an apparent hyperacidity, due really, however, to a hypersecretion. Inasmuch as no case has ever been reported with an acidity above 150, or the upper limit of undiluted gastric juice, Rubow concludes that hyperacidity does not exist. As stated above, Bickel also found the gastric juice in the human being remarkably constant as to acidity. As shown in Table 2, at least some cases of hyperacidity are simple hypersecretion, the calculated acid as already stated being within normal limits. Since using the present modification of the Sahli meal I have been unable to demonstrate beyond doubt any case of true hyperacidity. For instance, in one case the first test meal resulted in a calculated acidity of 356. A second and third test meal gave figures of 92 and 100, respectively, so that the method

4. Rubow: Arch. f. Verdauungskr., 1907, xiii, 577.

was unquestionably at fault; i. e., the emulsion had possibly been destroyed so that the fat formed a layer at the top while the lower thinner fluid passed through the pylorus. While, therefore, I am certain that the diagnosis, "hyperacidity," ought to be made very much less frequently than at present, very much more evidence will have to be produced before the word is entirely dropped.

TABLE 4.—HYPOACIDITY

Acidity of undiluted gastric juice varies normally between 120 and 150 (calculated in terms n/10 NaOH).

Hypoacidity is present when acidity is less than 100.

Case Number.	Total Amount in Stomach = *T.C.*	Ratio of Fat in Meal to Fat in Stomach Contents = *F.:f.*	Calculated Amount of Test-Meal in Aspirated contents = *T. M.*	Calculated Amount of Gastric Juice in Stomach Contents = *G. J.*	Secretory Quotient = *Q.*	Motility.	Titrated Acidity.	*Calculated Acidity of Undiluted Gastric Juice.*	Diagnosis.	Remarks.
16	166	2.7:1.4	86	80	0.95	0.7	26	54	Chronic gastritis.	Mucus++.
16	197	2.9:2.0	136	61	0.45	0.46	28	90	Chronic gastritis.	250 c.c. equal parts condensed milk and water given as test meal.
17	284	2.8:1.4	142	142	1.0	0.45	32	68	Chronic gastritis.	Mucus++.
18	97	2.5:1.4	54	43	0.8	0.78	20	45	Amyloidoses.	
19	55	2.8:1.5	29	26	0.9	0.88	20	41	Tb. ulcer of duodenum.	
20	123	?	64	59	0.92	0.78	7	15	Simple achylia gastrica.	
20	170	2.4:1.0	70	100	1.4	0.77	4	7	Simple achylia gastrica.	Removed in 30 minutes.
21	200	2.4:1.3	119	81	0.68	0.6	4	10	Simple achylia gastrica.	Removed in 30 minutes.
21	233	2.2:1.4	149	84	0.57	0.5	4	11	Simple achylia gastrica.	Removed in 30 minutes.
22	141	3.0:1.9	89	52	0.58	0.7	8	22	Simple achylia gastrica.	
22	100	2.6:1.8	69	31	0.45	0.77	8	26	Simple achylia gastrica.	
23	365	3.0:1.6	195	170	0.87	0.25	28	60	Carcinoma of pylorus.	
24	194	2.5:1.9	147	47	0.32	0.51	20	50	Carcinoma of lesser curvature.	
25	70	2.2:1.6	51	19	0.37	0.8	4	15	Carcinoma.	
26	300	?	186	114	0.6	0.38	..	16	Carcinoma of fundus.	

The opposite variation, or "hypoacidity," is represented in Table 4. By uncomplicated hypoacidity we mean that, no matter what the titrated acidity is, on calculating the real acidity of the undiluted gastric juice, we find it below 100; i. e., the stomach is secreting a more watery fluid than normal.

This was found to be the case quite consistently in at least three conditions, viz.: chronic gastritis, achylia gastrica simplex and in some carcinomas. To take the most pronounced cases first, those of achylia

gastrica, it was found that on titration the acidity varied between 4 and 8 (it was often necessary to aspirate in thirty minutes on account of the hypermotility), and that the amount of gastric juice secreted was generally normal, but the calculated acidity 26 or less. In other words, the gastric mucosa in some cases secretes almost pure water.

This seemed to indicate an error in the method, as both Martius[5] and Einhorn[6] define achylia as a condition in which there is entire absence of gastric secretion. A review of the literature, however, shows that the same condition has been found before not only in achylia, but in other conditions. It has been shown experimentally that the secretion of water, or hydrochloric acid, and of pepsin are three quite distinct functions of the gastric glands. Schiff[7] showed that in pathologic conditions there need be no parallelism between the variations of pepsin and hydrochloric acid; that by injecting pilocarpin the water could be increased, while acid diminished and pepsin remained constant. Schneyer[8] found that by stimulating the vagus of a fasting dog 3 to 15 c.c. of gastric juice flowed out, but without hydrochloric acid or pepsin, while if the animal had been fed within twenty-four hours both hydrochloric acid and pepsin were present. Roth and Strauss[9] showed that not only were hydrochloric acid and pepsin secretions distinct functions, but that water secretion was due to two distinct causes: (1) to osmotic phenomena in which the gastric mucosa acts as an animal membrane, and (2) to the specific activity of the gastric glands producing a "diluting" secretion often in defiance of the laws of osmotic pressure; and, furthermore, that in achylia gastrica, even when hydrochloric acid and pepsin secretions have ceased, this diluting fluid is still poured out. This is the condition indicated in Table 4. Hydrochloric acid was almost entirely absent, pepsin (not represented in the table) greatly diminished, while practically water alone was secreted. It will be noted that the quantity of water in most cases was practically normal; i. e., the secretory quotient was above 0.75.

In the case of chronic gastritis given here, the same condition was found, but to a less extent; i. e., the calculated acidity was higher (between 54 and 90), but still below normal. That this, too, is the usual condition in gastritis is shown by the work of Bickel[10] on dogs with

5. Martius: Achylia Gastrica. Ihre Ursache und Ihre Folgen. Reprint, 1897, p. 4.
6. Einhorn: Arch. f. Verdauungskr., 1896, i, 454.
7. Schiff: Arch. f. Verdauungskr., 1900, vi, 107.
8. Schneyer: Ztschr. f. klin. med., 1897, xxxii, 13.
9. Roth and Strauss: Ztschr. f. klin. Med., 1899, xxxvii, 144.
10. Bickel: Arch. f. klin. Med., 1906, lxxxix, 34.

Pawlow fistulas. Here, too, after irritation of the mucosa by local applications of alcohol and silver nitrate solutions, the amount of gastric secretion was found to be normal, but the hydrochloric acid content diminished.

TABLE 5.—HYPOSECRETION

Normal secretory quotient (Q) varies between 0.75 and 1. Hyposecretion is present when Q is less than 0.75.

Case Number.	Total Amount in Stomach = TO.	Ratio of Fat in Meal to Fat in Stomach Contents = $F:f$.	Calculated Amount of Test Meal in Aspirated Contents = $T.M.$	Calculated Amount of Gastric Juice in Aspirated Contents = $G.J.$	Secretory Quotient = Q.	Motility.	Titrated Acidity.	Calculated Acidity.	Diagnosis.	Remarks.
8	102	3.0:2.1	71	31	0.44	0.76	28	92	?	250 c.c. equal parts condensed milk and water given.
8	100	3.3:2.5	76	24	0.31	....	28	112	?	
9	120	3.4:2.6	107	32	0.3	0.65	34	140	Pernicious anemia.	
9	180	3.1:2.4	146	43	0.3	0.51	30	132	Pernicious anemia.	
10	150	3.2:2.8	131	19	0.14	0.56	20	158	Pernicious anemia.	
10	210	2.2:1.6	153	57	0.37	0.49	44	162	Pernicious anemia.	
11	132	2.1:1.6	100	32	0.32	0.67	24	99	Pernicious anemia.	
12	112	2.0:1.6	90	22	0.24	0.7	30	153	Connective tissue infiltration of walls (old ulcer).	
13	75	1.9:1.6	63	12	0.2	0.7	?	?	Carcinoma of fundus.	Large amount of lactic acid.
14	235	2.8:2.1	197	58	0.3	0.53	6	26	Pernicious anemia.	
15	228	2.1:1.6	173	55	0.31	0.42	38	157	Pernicious anemia.	Removed in 35 minutes.
15a	152	?	119	33	0.28	0.52	29	133	Carcinoma.	

A third condition in which the calculated acidity was subnormal was carcinoma. Here, however, the total amount of secretion was lowered; i. e., the secretory quotient was small. Now, according to Schiff,[7] the order in which the different functions are affected and disappear is: first, the hydrochloric acid secretion; second, the pepsin secretion; third, the diluting secretion. When only the first two are affected, as in achylia simplex, it is possible that there is only a functional disturbance of the mucosa, but when the diluting secretion is diminished we may be certain that a real atrophy of the mucosa is present and that the amount of the diminution measures the amount of atrophy. For example, in an instance of carcinoma of the pylorus (Case 23) the calculated acidity was 60 and the secretory quotient 0.87. In Case 24, a diffuse carcinoma of the lesser curvature (in which an exploratory laparotomy was

done), the calculated acidity was 50 and the secretory quotient 0.32. Evidently the difference was due to the variations in the area involved. The motility in these cases follows the known rules: it is good in some and impaired in others, according to the situation.

In Table 5 is shown the series of cases in which the amount of water secreted was uniformly below normal, but the percentage of acid was normal, the so-called hyposecretion.

Taking the cases of pernicious anemia, we find that the amount of secretion was the factor most affected, viz.: a secretory quotient varying between 0.14 and 0.37, with normal acidity. This combination accounts for the low titrated acidity which we find in pernicious anemia; it forms a sharp contrast to the conditions in hypersecretion, given in Table 1.

Another cause for a low titrated acidity is hypoacidity, such as that which occurs in chronic gastritis and achylia, as seen in Table 4; these two conditions have, as we have seen, an entirely different significance functionally, though in both there is a low apparent acidity. If we accept the above-mentioned assertions of Schiff, that the last function of the mucosa to suffer is the secretion of water, the observation that it is here diminished in contradistinction to the condition observed in achylia, would suggest the conclusion that here the local process (atrophy) is more advanced than in the latter, or that the condition of the blood serum was such as to diminish the secretion. An inconsistency for which I can not account is the normal calculated acidity, which is contrary to what one might expect if one assumes that the acid secretion is the first to suffer. That the acid also is diminished in the more severe cases is shown by the figures in Case 14, an advanced case with marked cord changes. Here not only was the quantity of fluid diminished, but the quality impaired; i. e., a calculated acidity of 26. Here the atrophy was far advanced, as pathologic examination showed.

Patient 12 complained of pain, vomiting and emaciation. Motility and calculated acidity were normal, so that the low acidity was due to hyposecretion, the quotient being only 0.24. In the light of the above cases, the only justifiable diagnosis was atrophy, though one of probable carcinoma was made. Laparotomy disclosed simple connective-tissue infiltration of over two-thirds of the stomach from a healed ulcer, with atrophy of a considerable part of the mucosa involved, a condition just such as the clinical observations might have suggested.

Case 8 was an undiagnosed case, apparently not a carcinoma, more probably an arteriosclerotic atrophy, to judge from the hyposecretion.

The above are some of the more interesting considerations suggested by a study of the results obtained by this method. That they have a solid basis is shown by their experimental verification.

The method does, however, fail occasionally, probably for the reason that the emulsion is destroyed. Failure is particularly liable to occur under the following circumstances:

1. In cases in which there is low acidity and hypermotility. In such cases there will be so little fluid left in the stomach in fifty minutes that no accurate fat determination can be made. When such a condition is suspected, it is best to aspirate in thirty minutes.

2. In cases of gastritis in which there are very large amounts of mucus which destroys the emulsion and by rising to the surface of the Babcock bottles obscures the readings.

3. In cases of greatly impaired motility owing to the difficulty of completely emptying the stomach preliminary to lavage.

Even where it fails it still, however, offers as much information as the ordinary Ewald test breakfast.

SUMMARY

1. The method here proposed for the study of the gastric functions is a modification of the Sahli test meal, consisting of one-third condensed milk and two-thirds water, the object being to obtain a stable emulsion of fat. With a very little extra work we can calculate the amount of gastric juice in the stomach at the time of aspiration, and so determine its real acidity as well as the gastric motility, etc.

2. We have, then, definite standards for comparison which enable us to make more accurate functional diagnoses than are at present possible otherwise.

3. Among the advantages of this meal over the Ewald and Riegel meals is the consideration that the conditions of most of the gastric functions may be determined by a single aspiration. Its advantages over the Sahli meal are its constancy of composition, the ease with which it may be prepared and administered, its strong secretory stimulating powers, and the stability of the emulsion.

190 State Street.

A STUDY OF THE BLOOD IN PERTUSSIS *

JOHN ALBERT KOLMER, M.D.
PHILADELPHIA

The number of investigations into the state of the blood in pertussis is comparatively small, but there exists a striking uniformity in the results obtained, though accuracy in a review of such investigations is, unfortunately, in some details difficult, because of the varying classifications of the leucocytes which have been adopted.

While the blood changes in pertussis are interesting in themselves, the diagnostic value of the interpretation placed on these changes by the various authors lends additional interest to this study.

With few exceptions, a leucocytosis and lymphocytosis have been noted early in the disease, and diagnostic value has been attributed to their presence. Recently more careful study has well-nigh established a definite series of blood changes in this disease and has demonstrated the value of a blood examination in the early diagnosis of pertussis.

The following is merely a brief review, the literature having been quite well covered recently by Barach.[1]

In 1897 Fröhlich,[2] the first to call attention to the blood changes in whooping cough, found a leucocytosis in 55 cases and a lymphocytosis in the fifteen differential counts made. The next year Meunier[3] found a leucocytosis in 30 cases, and, from ten differential counts, concluded that all forms of leucocytes were affected in this disease except the eosinophiles. De Amici and Pacchioni[4] in a study of 18 cases, Stengel and White[5] of 3, Muggia and Bertolotti[6] of 25, Grulee and Phemister[7]

---

*Read by invitation before the Philadelphia Pediatric Society, Nov. 10, 1908.

1. Barach, J. H.: Morphology of the blood in pertussis. THE ARCHIVES INT. MED., 1908, i, 602-604.

2. Fröhlich: Beitrag zur Pathologie des Keuchhustens. Jahrb. f. Kinderh., 1897, xliv, 53.

3. Meunier, H.: De la leucocytose dans la coqueluche. Compt. rend. Soc. de biol., 1898, 103-105.

4. De Amici, G., and Pacchioni, D.: Sulla leucocitosi nella pertosse. Clin. Med., 1898, xxxviii, 51-61. La leucocytose dans la coqueluche. Rev. mens. d. mal. de l'enf., 1900, xviii, 58. (Abstr.) Ueber leucocytose beim Keuchhusten. Arch. f. Kinderh., 1902, xxxiv, 305-306.

5. Stengel, A., and White, C. Y.: Blood in infancy and childhood. Univ. Penn. Med. Bull., 1902, xiv, 310-325.

6. Muggia (A.) et Bertolotti (M.): Ozonoterapie e reperti ematologici nei bambini affetti da pertosse. Pediatria, Napoli, 1904, Series 2, ii, 875-889.

7. Grulee, C. G., and Phemister, D. B.: The leucocytes in whooping cough. Arch. Pediat., N. Y., 1905, xxii, 595-599.

of 15, Churchill[8] of 28, Barach[1] of 30 cases, and Crombie[15] in an analysis of 112 cases, all found a leucocytosis and lymphocytosis, beginning in the catarrhal stage, increasing in severity with the paroxysmal and then decreasing until the normal was reached.

Mosenthal[9] found the leucocytes approximately double the normal in the catarrhal stage, with less marked changes in the convulsive period. Cabot[10] reported two cases of pertussis-pneumonia which, from the high leucocytosis and lymphocytosis, led him to believe the cases atypical pertussis. Steven[11] reports a similar case.

Cima[12] found a higher leucocytosis in pertussis than in other infectious diseases. On the other hand, Carriere[13] found a higher leucocytosis in bronchitis, and Wanstall[14] found an absence of leucocytosis in 5 cases in the catarrhal stage of pertussis, but, in 11 out of 14 cases, demonstrated the presence of a lymphocytosis.

During the latter part of the summer and early autumn of 1908, I had the opportunity of studying 27 cases in St. Vincent's Home and Maternity Hospital from the beginning to the end, having full control of my patients. Two cases were fortunately, though by accident, examined in the precatarrhal stage. It was soon evident that there occurred an appreciable change in the blood formula early in the disease. But, in order that these changes may be considered as possessing diagnostic value, it was necessary to determine a more or less normal standard for institutional children where hygienic conditions generally are not so good as in private homes and where the children are more likely to be poorly developed and anemic. Accordingly the object of my study was:

1. To determine what may be considered as a working standard for the total number of leucocytes and the various proportions of the leucocytic elements in the blood of institutional children of various ages.

---

8. Churchill, F. S.: Diagnostic value of the leucocyte formula in pertussis. Jour. Am. Med. Assn., 1906, xlvi, 1506.

9. Mosenthal, H. O.: Leucocyte count of normal "institutional" children and those suffering with pertussis. Arch. Pediat., xxv, 1908, 831.

10. Cabot, R. C.: Clinical Examination of the Blood; ed. 5, New York, Wood, 1904, p. 220.

11. Steven, A.: Bronchopneumonia. Lancet, London, xx, 791.

12. Cima, F.: La Pediatrica, 1899, vii, 261.

13. Carriere, G.: Le sang dans la coqueluche et dans l'adénopathie tracheobronchique. Gaz. hebdom. de méd. et de chir., 1902, xlix, 127.

14. Wanstall, A.: Pertussis with special reference to its early diagnosis, from the blood findings. Am. Med., 1903, v, 62-65.

2. To ascertain if it were possible to diagnose whooping-cough, with some degree of certainty, early in its course and in atypical cases by a study of the blood.

3. To study the blood in conditions resembling the catarrhal stage of whooping-cough to ascertain if the blood changes peculiar to this infection occur in them also. The opportunities in this direction were limited mainly to bronchitis and laryngitis.

4. To study the blood in cases of pertussis modified by complications. The opportunities in this direction comprised two cases of pneumonia and two cases of convulsions, and one case, each, of impetigo contagiosa, ecthyma and Vincent's angina.

It is plain that if we could by some means diagnose whooping-cough early in the catarrhal stage, which is generally impossible by the symptoms alone, it would be of great advantage especially from the standpoint of prophylaxis. It is most desirable to isolate children suffering with pertussis as early as possible, for without doubt the disease is very infectious during the catarrhal stage[15] and scarcely less so during the paroxysmal stage. The importance of early diagnosis and isolation is emphasized in institutions for children where the inmates are more or less closely associated and the spread of the infection correspondingly facilitated. Again, many cases pursue an atypical course in which there is either no whooping or else a paroxysmal stage of short duration. Such cases were found to occur most frequently in infants. When we remember how disastrous pertussis is among the young and how helpless we are in ameliorating the symptoms and preventing fatal complications, it behooves us to avail ourselves of every means whereby the disease may be early diagnosed and its victims promptly isolated.

Due care was exercised in avoiding digestive leucocytosis, which especially affects the lymphocytes. Wright's stain was used throughout, being very simple and quite satisfactory. In most instances two leucocyte counts were made and two smears examined in each case at every examination.

CONTROL CASES

Early in this work I was impressed with the fact that a hazy idea of what constituted the normal blood picture in children, especially children of the type we were examining, would not suffice if one was to attempt making an early diagnosis of whooping-cough by an examination of the blood. It was necessary to know with some definiteness what constituted normal limits and what to regard as pathologic. I knew in a general way that the blood of institutional children and those

raised amid poor surroundings, as in the slums of a large city, differs from the blood of children reared in our better private homes. Such common affections as rickets, chronic glandular enlargements, intestinal disorders and congenital syphilis tend to upset the leucocytic formula, mainly affecting those cells with which we are most interested, the lymphocytes. As a general rule most institutional children suffer with rickets of varying degree of severity, many have variously sized glandular enlargements and intestinal disorders are very common, especially in artificially fed infants. With all these things to be remembered one would naturally think that blood examinations were not worth while. I believe their importance, however, with the exception of age, is a little exaggerated. This appears, at any rate, to be true of the following cases which were selected more or less at random from the children of St. Vincent's Home and belong to the usual institutional type. We believe that the results of these blood examinations would apply also to children as met in the ordinary dispensary practice.

TABLE I.—BLOOD EXAMINATION OF NORMAL INSTITUTIONAL CHILDREN; AGE, 3 TO 12 MONTHS

No.	Age, Mos.	Leucocytes.	Lymphocytes. Small.	Lymphocytes. Large.	Transitionals.	Polymorphonuclears.	Eosinophiles.	Mast Cells.
1	3	7,800	44	15	3.57	36.42	1.07	.0
2	3	9,360	47.5	14.1	3.2	32.6	2.5	.1
3	6	8,800	54.88	11.2	3.12	26.4	4.4	.0
4	6	16,880	48.86	6.81	1.59	41.14	1.59	.0
5	6	10,240	26.81	24.09	3.63	43.25	2.22	.0
6	6	9,680	59.62	13.33	0.74	25.57	0.74	.0
7	6	10,640	44.52	9.65	0.34	42.07	3.1	.34
8	7	12,000	27.39	14.21	1.35	53.55	3.57	.0
9	12	12,000	42.31	16.61	1.23	38.01	1.23	0.
10	12	12,000	58.82	10.29	1.47	28.24	0.88	.29
Av'ge.	5½	10,900	45.47	13.53	2.02	36.78	2.13	.07

TABLE II.—BLOOD EXAMINATION OF NORMAL INSTITUTIONAL CHILDREN; AGE, 1 TO 2 YEARS

No.	Age, Yrs.	Leucocytes.	Lymphocytes. Small.	Lymphocytes. Large.	Transitionals.	Polymorphonuclears.	Eosinophiles.	Mast Cells.
1	1½	10,160	37	11	2	48.33	1.66	.0
2	1¼	8,720	22.22	22.96	1.11	51.85	1.85	.0
3	1⅓	10,900	31.83	13.03	1.81	51.51	1.51	.3
4	2	14,000	48	11	.5	39.5	2	.0
5	1⅓	11,200	48.33	16.66	.66	34.01	.66	.0
6	1	12,000	58	10.85	1.42	28.72	1	.0
7	2	9,800	48.12	15.79	3.15	30.52	2.1	.32
8	2	12,000	54	9.75	1.25	43.5	1.5	.0
9	2	17,000	40.66	11.66	2.33	45	.34	.0
10	1½	10,500	27.42	15.92	1.11	53.7	1.85	.0
Av'ge	1½	11,690	41.55	13.86	1.53	42.66	1.45	.03

TABLE III.—BLOOD EXAMINATION OF NORMAL INSTITUTIONAL CHILDREN; AGE, 2 TO 3 YEARS

No.	Age, Yrs.	Leucocytes.	Lymphocytes. Small.	Lymphocytes. Large.	Transitionals.	Polymorphonuclears.	Eosinophiles.	Mast Cells.
1	3	11,880	42.22	8.88	.83	45.56	2.5	.0
2	2	14,000	27.1	7.54	.52	63	1.84	.0
3	2½	12,160	38.41	12.38	1.58	43.81	3.17	.63
4	3	16,000	27	10.25	1	59.5	2	.25
5	2	10,880	44.37	12.91	1.45	34.54	2.29	.02
6	3	16,100	29.19	7.14	.4	61.63	1.63	.0
7	1⅓	12,500	32.89	11.51	1.31	52.13	2.1	.26
8	3	14,320	40.9	7.57	.6	48.78	2.14	.0
9	1⅔	11,900	38.15	9.47	1.84	49.45	1.05	.03
10	2	12,100	35.4	15.6	.8	47.4	.8	.0
11	2	10,600	27.93	7.58	1.72	57.24	5.52	.0
12	2	11,200	36.03	11.85	1.11	50.26	.74	.0
13	1⅔	11,750	25	9.54	1.81	61.81	3.18	.0
14	3	12,100	40.33	7	.66	50	2	.0
15	1⅔	11,500	45.55	22.58	1.48	28.53	1.48	.37
16	3	12,200	37.02	8.37	.54	52.72	.54	.81
17	3	11,800	35.76	10	1.15	49.63	3.45	.0
18	2	11,600	33.33	10.6	.6	53.34	2.12	.0
19	2½	11,400	35.92	8.63	1.36	48.18	5.9	.0
20	2½	12,300	36.01	10	1.33	50	2.66	.0
21	2½	11,400	35.55	21.11	1.11	41.48	.74	.0
22	3	10,900	31.31	10.87	.71	55.87	1.42	.0
23	2½	14,200	39.59	16.32	.83	40.81	2.44	.0
24	1⅔	11,600	47	12.08	.41	40	.41	.0
25	1⅔	11,900	27.27	9.09	1.21	58.8	3.03	.6
Av'ge	2¼	12,300	35.57	10.73	1.15	49.93	2.3	.01

TABLE IV.—BLOOD EXAMINATION OF NORMAL INSTITUTIONAL CHILDREN; AGE, 3½ TO 5 YEARS

No.	Age, Yrs.	Leucocytes.	Lymphocytes. Small.	Lymphocytes. Large.	Transitionals.	Polymorphonuclears.	Eosinophiles.	Mast Cells.
1	3½	14,080	18.93	12.8	.53	62.68	4.53	.53
2	3½	10,500	27.41	11.63	.64	58.06	2.26	
3	3	10,400	23.01	9.81	.75	63.04	2.64	.75
4	3	9,500	27.77	13.33	.55	55.55	2.24	.55
5	4	12,800	30.86	8.69	.43	56.10	3.91	
6	4	16,400	12.22	9.63	.74	75.52	1.85	.04
7	4	6,400	35.43	6.31	.68	56.14	1.4	.03
8	4	9,760	39.66	6.66	.66	51	2.02	.0
9	4	11,500	36.08	7.8	.73	52.44	2.92	.02
10	4	9,680	25.72	7.5	1.07	62.5	3.21	.0
11	4	10,290	25.66	6.66	.33	65	3	.33
12	4	9,760	16.66	7.71	1.11	72.3	2.22	.0
13	4	11,800	23.45	10	1.17	64.20	1.18	.0
14	4	11,000	27.54	13.89	.61	55.93	2.03	.0
15	4	10,800	28.5	8.6	.5	58.2	4.1	.0
16	4	10,500	31.31	9.33	1.33	52.33	5.66	.33
17	4	9,900	25	7.85	.71	62.28	3.57	.58
18	5	10,560	28.34	4.33	1	65	1.33	.0
19	5	9,520	30.21	5.71	.35	61.22	2.5	.0
20	5	11,400	38.57	12	1.13	45.91	2	.28
21	5	11,120	25.28	5.66	.66	67.03	1	.0
22	5	11,400	38.5	5.65	.80	51.33	3.71	.0
23	5	10,100	24.52	10.64	.32	61.61	2.9	.0
24	5	9,900	29.35	12.9	.64	54.85	2.25	.0
25	5	12,250	30.67	11.46	.73	54.14	2.92	.48
Av'ge	4¼	10,846	27.62	9.06	.72	59.37	2.73	.15

TABLE V.—SUMMARY OF BLOOD EXAMINATION IN CONTROL CASES

Age, Yrs.	Leucocytes.	Lymphocytes. Small.	Lymphocytes. Large.	Transitionals.	Polymorphonuclears.	Eosinophiles.	Mast Cells.
3-12 mos.	10,900	45.57	13.53	2.02	36.78	2.13	.07
1-2 yrs.	11,600	41.55	13.86	1.53	42.66	1.45	.03
2-3 yrs.	12,300	35.57	10.74	1.15	49.94	2.3	.01
3½-5 yrs.	10,800	27.62	9.06	.72	59.37	2.73	.15

One must examine the tables and not the averages to appreciate the range of variability in the percentages of the various leucocytic elements. Tentative examination will show the following points:

1. The number of leucocytes does not change materially with age up to five years. One is apt to find a lower count in an artificially fed infant than he would in a healthy breast-fed infant of the same age. No. 4, Table 1, was from a well-nourished breast-fed baby. I myself do not consider any such young children to have a leucocytosis unless the count is over 12,000 leucocytes per cubic millimeter.

2. The percentage of lymphocytes, both the small and large varieties, decrease as age advances. In well-marked cases of rickets a large percentage of large lymphocytes were found. Comparison with the blood of healthy private home children shows, as a general rule, a lower percentage of lymphocytes than is found in the blood of less fortunate children.

3. A fair percentage of basophiles or "mast" cells were found. Ewing has stated that these cells are generally absent in the blood of healthy children.

No blasts were encountered; a few phlogocytes or irritation forms of lymphocytes were seen, as were also many bilobate and "basket" cells.

While it is well to remember the range of variability in the percentages of the different leucocytes even at the same age, one must adopt a more or less arbitrary working standard. The percentage of lymphocytes is of most interest in relation to pertussis. The percentages used in this work are those given in the summary of the control cases.

PERTUSSIS CASES

The aim was to have cases of coughing reported at once and a blood examination made. Consequently most patients were examined quite early in the catarrhal stage. In a few instances the lymphocytosis was slight and a provisional diagnosis made. In the majority of cases there was an early and well-marked leucocytosis mainly affecting the small lymphocytes. At first there is an absolute increase in all the leucocytic elements. Soon the percentage of lymphocytes become higher and higher as the disease progresses. This early lymphocytosis is of most importance and, I believe, possesses a distinct diagnostic value many days before the true nature of the infection has asserted itself. The changes in the blood formula, while in most instances appreciable, were not so great but that a careful examination and due consideration of age and other modifying influences were necessary. Two patients were fortunately examined in the precatarrhal stage. Patient 8 was examined

for a slight cough, which cleared up entirely shortly afterward. About ten days later he recommenced coughing and an examination justified a diagnosis. In about eleven days he began to whoop. Patient 12 was examined to ascertain the presence of an eosinophilia in a suspected lumbricoides and oxyurides infection. This accounts for the large percentage of eosinophiles in this case.

All patients, except one, were examined in the catarrhal stage. Another examination was made during the height of the paroxysmal stage. A third count was made in the period of marked improvement when the children were coughing hard, but not whooping. A final examination was made on the average of about two months from the time of the paroxysmal stage.

TABLE VI.—BLOOD EXAMINATION OF PERTUSSIS PATIENTS IN PRECATARRHAL STAGE

No.	Name of Patient.	Age, Yrs.	Leucocytes.	Lymphocytes. Small.	Lymphocytes. Large.	Transitionals.	Polymorphonuclears.	Eosinophiles.	Mast Cells
8	John L.	4	14,000	45.24	6.76	2.7	41.24	3.9	.15
12	Jennie McB. ..	5	15,600	42.78	3.71	.75	37.9	14.72	.13
Average			14,800	44.01	5.23	1.72	39.57	9.31	.14

TABLE VII.—BLOOD EXAMINATION OF PERTUSSIS PATIENTS IN CATARRHAL STAGE

No.	Name of Patient.	Age, Yrs.	Leucocytes.	Lymphocytes. Small.	Lymphocytes. Large.	Transitionals.	Polymorphonuclears.	Eosinophiles.	Mast Cells
1	Annie Q.	1¼	16,000	52.9	18.62	3.91	20.62	3.9	.05
2	Lewis M.	Not taken							
3	Leo W.	4½	15,000	35.29	11.76	1.96	47.05	3.92	.02
4	Martin F.	2	14,000	46.11	16.43	2.02	31.5	3.5	.43
5	Katie D.	3	14,500	49.04	10.46	1.56	36.13	2.03	.89
5	(7 days later).		16,000	63.98	3.62	3.88	35.13	2.59	.8
6	Etta D.	3	.....	48.97	10.46	1.56	36.13	2.03	.89
7	Francis S.	1	13,000	46.76	5.88	2.94	42.45	1.47	.49
8	John L.	4	16,000	54.6	10.9	1.04	29.97	3.4	.08
9	Sophie R.	2½	28,000	61.39	3.62	.51	31.09	2.33	1.03
10	Margaret	2	19,000	57.51	9.56	2.87	27.65	1.43	.89
11	Eliz. M.	1½	17,500	48.75	10.61	3.4	33.71	2.47	1.05
12	Jennie McB. ..	5	.....	54.22	6.36	1.81	28.4	9.09	.03
13	Francis	1½	15,000	46.07	6.	1.27	43.7	2.	.9
14	Walter	2	16,900	48.94	9.71	3.41	34.8	2.63	.5
15	Tossie	2	12,500	46.93	5.75	2.12	38.52	5.45	.21
16	Eliz. B.....	2	Not taken.						
17	Katie P.	2¼	13,500	47.81	6.87	2.47	35.	7.81	.04
18	Alice.....	1	Not taken.						
19	Leo B.	2	14,900	47.94	6.78	1.48	37.51	5.41	.87
20	Charles L.	2	21,520	44.4	8.7	1.	39.3	6.2	.3
20	(3 da. later)..	.	22,600	49.14	10.71	2.67	32.14	4.46	.89
21	Edith	3½	16,000	52.42	9.65	.69	35.17	2.07	.0
22	Cath. H.	2	17,800	34.7	10.3	.69	51.	3.3	.0
23	Ikey	5/6	18,000	51.62	14.32	2.43	29.73	1.62	.27
24	Francis D. ...	1¼	14,500	48.17	15.44	1.97	33.8	.28	.28
25	Francis H. ...	4	15,200	44.64	13.39	1.96	36.6	2.7	.71
26	John M.	3	19,000	47.69	10.79	1.28	37.69	1.79	.76
27	Jno. McC.....	5/12	Not taken.	Out patient department.					
Average			16,800	49.19	9.83	2.03	34.98	3.35	.53

TABLE VIII.—BLOOD EXAMINATION OF PERTUSSIS PATIENTS IN PAROXYSMAL STAGE

No.	Age.	Leucocytes.	Lymphocytes. Small.	Lymphocytes. Large.	Transitionals.	Polymorphonuclears.	Eosinophiles.	Mast Cells
1	1¼ yrs.	25,000	63.4	6.4	1.4	27.4	.8	.6*
1	(2 da. later)	26,240	80.35	3.57	1.56	11.17	2.9	.37
2	1 yr.	24,900	61.07	9.01	2.34	24.07	2.39	1.21**
3	4½ yrs.	.....	70.41	9.31	1.48	14.53	3.4	.86
4	2 yrs.	29,000	63.9	10.16	2.47	21.13	1.46	.87
5	3 yrs.	16,000	63.98	3.62	3.88	25.13	2.59	.8
6	3 yrs.	17,000	62.5	8.34	3.05	22.83	2.94	.33
7	1 yr.	22,000	60.38	14.08	1.81	21.76	1.07	1.†
8	4 yrs.	23,000	71.84	9.77	2.29	11.49	3.45	1.15
9	2½ yrs.	.....	69.41	5.3	3.4	18.5	2.36	1.02
10	(Taken home.)							
11	1½ yrs.	21,000	60.	6.06	2.43	29.4	2.03	.06
11	(4 da. later)	20,000	65.6	8.	1.5	20.4	3.5	1.
12	5 yrs.	19,000	58.5	8.3	.6	29.	3.5	..
13	1½ yrs.	25,000	66.07	6.	1.27	23.7	2.	.9
14	2 yrs.	23,000	65.09	6.95	1.52	24.35	1.52	.65
15	2 yrs.	21,600	59.31	7.51	3.01	27.61	2.46	.09
16	2 yrs.	24,700	62.89	8.62	1.47	23.48	3.46	.08
17	2¼ yrs.	23,700	67.41	5.71	1.02	23.	2.38	.46
18	1 yr.	.....	65.41	6.41	1.78	24.01	2.38	.19
19	2 yrs.	26,500	71.04	5.89	2.63	17.53	1.89	1.01
20	2 yrs.	28,000	59.56	5.31	1.46	32.25	2.31	.09
21	3½ yrs.	11,000	52.4	10.	.8	34.	2.4	.4
22	2 yrs.	24,500	69.33	8.27	1.03	19.65	1.72	.0
23	10 mos.	28,500	75.47	9.54	.68	12.5	1.81	.0
24	1¼ yrs.	14,400	54.46	12.22	1.66	28.33	3.33	.0
25	4 yrs.	22,000	47.15	9.77	.88	40.88	.44	.88
26	3 years.	14,000	45.34	10.22	1.33	38.22	4.	.88
27	5 mos.	19,200	57.14	15.23	.95	24.36	2.38	.0
Average		22,000	63.19	8.19	1.77	23.92	2.35	.53

* Died of bronchopneumonia.
** Convulsions; death.
† Died of lobar pneumonia.

TABLE IX.—BLOOD EXAMINATION OF PERTUSSIS PATIENTS IN STAGE OF MARKED IMPROVEMENT

No.	Age.	Leucocytes.	Lymphocytes. Small.	Lymphocytes. Large.	Transitionals.	Polymorphonuclears.	Eosinophiles.	Mast Cells
3	4½ yrs.	13,000	39.53	4.65	1.05	49.12	3.5	.2
3	(1 wk. later)	13,760	33.18	18.18	1.36	44.09	2.26	.9
4	2 yrs.	19,800	36.	8.	2.1	47.	5.6	1.2
4	(1 wk. later)	13,920	33.75	6.66	.83	51.	6.35	.41
5	Taken home.							
6	3 yrs.	12,000	41.59	4.56	1.05	49.12	3.5	.2
6	(1 wk. later)	13,900	40.58	14.7	2.05	40.88	.88	.88
8	4 yrs.	13,500	50.6	4.24	1.51	42.12	1.21	.3
8	(1 wk. later)	20,320	25.2	12.	.8	59.2	2.4	.4
9	2½ yrs.	23,500	46.01	6.51	1.38	38.76	5.98	1.35
9	(1 wk. later)	15,100	32.07	13.2	2.61	48.69	2.64	.75
11	Taken home.							
12	5 yrs.	14,900	43.94	9.21	.52	42.1	3.42	.78
13	1½ yrs.	35,600	32.51	12.82	1.02	51.28	1.79	.51
14	2 yrs.	21,120	41.43	11.91	2.28	39.05	5.24	.09
15	2 yrs.	19,520	36.22	7.97	.32	52.9	2.26	.32
16	Taken home.							
17	2¼ yrs.	17,500	45.55	3.33	.55	42.33	7.07	1.11
17	(1 wk. later)	15,680	37.02	13.61	2.55	39.14	7.23	.42
18	Taken home.							
19	2 yrs.	14,900	34.48	15.51	1.03	46.55	1.03	1.38
20	2 yrs.	14,500	32.26	5.21	1.3	47.42	6.51	1.3
20	(1 wk. later)	14,800	34.08	18.86	1.72	40.24	4.75	.34
21	3½ yrs.	11,000	32.5	8.12	1.87	55.09	2.5	.02
22	Died. Convulsions and Vincent's angina.							
23	10 mos.	17,700	46.42	11.42	.36	40.	1.79	.0
24	1¼ yrs.	14,900	43.75	25.	1.25	26.	3.75	.25
Average		16,800	38.39	10.6	1.34	45.09	3.71	.55

TABLE X.—BLOOD EXAMINATION OF PERTUSSIS PATIENTS IN THE POST-PAROXYSMAL STAGE, TWO MONTHS

No.	Age, Yrs.	Leucocytes.	Lymphocytes. Small.	Lymphocytes. Large.	Transitionals.	Polymorphonuclears.	Eosinophiles.	Mast Cells.
3	4½	16,000	37.5	14.16	1.66	41.66	5	.0
4	2	12,400	43	7.91	1.25	45.83	2.08	.0
6	3	12,800	34	17.14	1.78	46.35	.71	.0
8	4	8,000	40.48	10.64	1.23	47.17	.85	.0
9	2½	19,000	32.62	9.23	1.23	55.38	1.23	.3
12	5	11,700	33.28	7.64	1.11	47.64	9.41	1.11
13	1½	15,000	35	12.6	.8	50	1.2	.4
14	2	15,000	40	6.75	.62	50.12	2.5	.0
15	3	20,000	41.66	12.5	2.08	42.09	.83	.83
17	2¼	13,000	27	12.5	.5	51.5	7	1.5
19	3	12,500	34.53	10.32	.32	53.54	1.29	.0
20	2	12,000	45.88	12.35	1.76	37.06	2.94	.0
Av'ge	..	14,000	37.07	11.14	1.19	47.36	2.92	.34

TABLE XI.—SUMMARY OF BLOOD EXAMINATIONS IN PERTUSSIS CASES

Stage.	Leucocytes.	Lymphocytes. Small.	Lymphocytes. Large.	Transitionals.	Polymorphonuclears.	Eosinophiles.	Mast Cells.
Precatarrhal	14,800	44.01	5.23	1.72	39.57	9.31	.14
Catarrhal	16,800	49.19	9.83	2.03	34.98	3.35	.53
Paroxysmal	22,000	63.19	8.19	1.77	23.92	2.35	.53
Marked improvement..	16,800	38.39	10.6	1.34	45.09	3.71	.55
Two months after....	14,000	37.07	11.14	1.19	47.36	2.92	.34

It may be well to note a few of the more important points demonstrated in the tables.

1. There is a slight leucocytosis and an absolute increased percentage of all forms even in the precatarrhal stage, judging from the examinations in the two cases. The number of leucocytes steadily increases in the catarrhal stage, reaches the climax in the paroxysmal stage and then falls by lysis. Barach[1] states that they reach normal proportions in a little over three months.

2. The lymphocytes follow a similar course. I do not think that one could always appreciate an increase in the precatarrhal stage, but certainly a lymphocytosis will be found in the catarrhal stage in the great majority of cases. This lymphocytosis reaches its climax in the paroxysmal stage and then gradually falls. The increased percentage of lymphocytes is absolute and not simply relative, as is frequently found in rickets. The cause of this phenomenon has been attributed to a congestion of the tracheobronchial glands.

3. The large lymphocytes run a more irregular course. In most cases a large percentage was found when the number of small lymphocytes was high. It will be noted that their percentage usually remains high for a time after the small lymphocytes begin to decrease.

4. The transitionals run a very irregular and unimportant course.

5. The percentage of polymorphonuclear neutrophiles is in most instances actually increased, but relatively they decrease as the lymphocytes go up. It is interesting to note how this relationship is changed in the complications of pertussis, notably lobar pneumonia, and in secondary infections.

6. The eosinophiles run a more typical course. During the catarrhal stage they are usually present in normal proportions, are relatively decreased in the paroxysmal stage, and in the postparoxysmal stage a mild eosinophilia sets in.

7. I have found that the basophiles begin to distinctly increase in the catarrhal stage and that the percentage remains higher than normal throughout the disease.

8. Many bilobate and "basket" cells were found, especially in the presence of a high lymphocytosis. No myelocytes were encountered.

DIFFERENTIAL DIAGNOSIS

Quite generally whooping-cough is not diagnosed early in its course, because it resembles an ordinary cough without expectoration, accompanied by a little fever. It may go on in this manner for a week to ten days, and even longer, before one's suspicion is aroused by a more incessant cough, injection of the conjunctiva and a tendency toward paroxysms of coughing. A few observers assert that the disease is most contagious in this period. Those who have had experience with many children living together, as in an institution, are well acquainted with the coughs that spring up every now and then, practically unaccompanied by systemic symptoms and often without positive signs on physical examination. Often such a cough clears up without treatment, and about just as often it hangs on for a long time despite treatment. I call particular attention to the table composed of such cases in which one examination was made and a negative diagnosis given. When the danger of whooping-cough infection is present, it is just such cases that arouse one's anxiety to know if they are ordinary coughs or genuine pertussis or if pertussis is developing during the course of such a chronic cough. The other cases were diagnosed by the subjective symptoms and physical examination. Case 3, diagnosed as one of bronchitis, is interesting in that the small lymphocytes kept on increasing and then began to fall. The child never whooped. It is debatable whether this case was not one of an atypical pertussis, as it is not infrequently encountered in very young children.

TABLE XII.—BLOOD EXAMINATION IN CASES OF COUGHS OTHER THAN PERTUSSIS

No.	Date.	Name of Patient.	Age, Yrs.	Leucocytes.	Lymphocytes. Small.	Lymphocytes. Large.	Transitionals.	Polymorphonuclears.	Eosinophiles.	Mast Cells.
CASE 1.—BRONCHITIS										
1	9/16	Eliz. E.....	4	11,000	40	3.5	.5	53.5	1.5	1
	9/28			9,500	40.9	9.54	1.36	40.9	6.86	.45
	10/2			9,500	35.93	14.37	.62	45.32	3.12	.62
CASE 2.—LARYNGITIS										
3	9/17	Kelly	1 1/6	9,000	39.79	7.19	1.25	50	1.56	.3
	9/20			9,500	40	6.5	1.5	48.53	3.4	.06
CASE 3.—BRONCHITIS										
5	9/19	Mary F....	11/12	9,000	22.22	7.12	1.94	61.11	6.68	.96
	10/24			21,200	54.44	29.45	2.44	10	3	.66
	10/26			20,000	69.74	13.33	1.28	14.1	1.54	.0
	11/1			10,000	57.82	19.13	.86	20.88	1.3	.9
CASE 4.—BRONCHITIS										
7	9/22	Nick	4	9,960	31.06	6.13	1.11	57.72	3.4	.58
	9/25			9,000	29.5	7.2	.9	57.8	4.5	.09
CASE 5.—BRONCHITIS										
9	9/24	Alice	¾	10,000	42.86	7.41	.96	46.77	1.29	.64
	10/2			14,800	35.25	12.5	1.75	46.75	3.12	.62
CASE 6.—BRONCHITIS										
14	9/25	Willie Y...	3	10,600	21.66	5.66	1.66	60.66	10	.33
	10/3			9,300	21.42	11.42	1.42	60.28	5.03	.42
CASE 7.—BRONCHITIS										
16	9/30	Harry S...	2½	12,720	26.19	17.14	3	51.78	1.42	.47
	10/2			12,000	20.49	16	2.33	58.63	2	.33
CASE 8.—BRONCHITIS										
19	10/2	Mary McC..	3	12,080	40.61	10.46	3.38	43.38	1.84	.3
	10/17			14,500	40.17	9.04	1.42	46.04	2.86	.47
	10/26			10,500	43.12	7.5	.62	45.31	2.19	1.25
MISCELLANEOUS COUGHS										
1	10/12	Eliz. E.....	4½	11,000	40.93	14.37	1.36	45.32	3.12	.62
2	9/17	John N....	3	12,900	33.33	15.15	3.33	46.97	.7	.5
4	9/19	Gert. A....	4	9,000	25.52	5.26	1.05	63.15	4.94	.05
6	9/20	John J.....	3½	9,500	45.61	7.85	.95	42.76	1.9	.71
8	9/22	Joseph G...	5	9,910	38.44	6.75	.54	51.35	1.62	1.3
10	9/24	Thomas H.	4	10,800	14.47	2.25	.64	75.8	6.16	.64
11	9/23	John H....	4	10,000	20.02	2.66	1.66	73.33	2	.33
12	9/23	William H.	5	10,500	28.18	5.24	2.03	63.63	.61	.3
13	9/23	George B...	2½	11,600	36.10	13.25	2.5	46.15	1.75	.75
15	10/2	Daniel O'C.	3	13,900	36.29	16.29	5.18	38.52	3.59	.11
17	10/2	James O'C.	3	14,800	35.25	12.5	1.75	48.25	1.5	.5
18	10/2	Annie N...	4	10,000	26.55	8.46	.38	64.23	.38	.0
20	10/31	John N....	5	11,800	18.5	11.5	1	65	3.5	.5
21	10/31	Clara E....	4	14,600	27.2	6.64	1.25	62	2.91	.0

A study of Table XII will show that in such cases there is little change in the blood. One notes in most instances a slight leucocytosis. Once in a while lymphocytes are slightly increased, and it is in such cases that a provisional diagnosis is made and the child isolated for a day or so, when a second examination is made. Quite generally there is a slight rise in the percentage of the eosinophiles, and I also draw attention to an appreciably increased percentage of mast cells.

COMPLICATIONS

A study of these presents much that is of interest.

Pneumonia

Bronchopneumonia is one of the most frequent complications. There was one typical case; another commenced as a bronchopneumonia, but soon developed into a lobar; both were fatal. Both cases developed at the close of the paroxysmal stage. The results of the blood investigations in the two cases are given together for comparison. Autopsies were held in both cases.

TABLE XIII.—BLOOD EXAMINATION OF PNEUMONIA PATIENTS

CASE 1.—BRONCHOPNEUMONIA

No.	Date.	Name of Patient.	Age, Yrs.	Leucocytes.	Lymphocytes. Small.	Lymphocytes. Large.	Transitionals.	Polymorphonuclears.	Eosinophiles.	Mast Cells.
1	8/12	Annie Q...	1¼	25,000	63.4	6.4	1.4	27.4	.8	.6
	8/13			29,700	68.40	3.36	1.41	21.27	5.47	.09
	8/14			26,240	80.35	3.57	1.56	11.17	2.9	.39

CASE 2.—LOBAR PNEUMONIA

7	9/10	Francis S..	1	22,000	60.38	14.08	1.81	21.76	1.07	1.
	9/12			24,000	34.78	10.43	2.6	48.26	2.6	1.3
	9/20			27,000	24.26	11.56	2.18	60.1	1.25	.62

In both cases an increased leucocytosis will be noted, especially marked in the lobar case. In the case of bronchopneumonia the small lymphocytes are absolutely increased, whereas in the case of lobar pneumonia the percentage of lymphocytes, on the other hand, steadily decreased while the polymorphonuclear neutrophiles were increasing.

Convulsions

There were two cases. In the first the convulsions succeeded on a violent paroxysm of coughing. Three hours later the child died. At autopsy the meninges on both sides were found much congested, and that was all.

TABLE XIV.—BLOOD EXAMINATION OF PATIENT WITH CONVULSIONS (CASE 1)

No.	Date.	Name of Patient.	Age, Yrs.	Leucocytes.	Lymphocytes. Small.	Lymphocytes. Large.	Transitionals.	Polymorphonuclears.	Eosinophiles.	Mast Cells.
2	7/25	Lewis M...	1	24,900	61.07	9.01	2.34	24.07	2.39	1.21
	7/27			29,000	59.56	5.31	1.46	32.25	1.31	.09

One blood count was taken during a quiet period shortly before death. The last count preceding the onset of the convulsions is given for comparison. It will be observed that with the convulsions there was an increased leucocytosis and a slight increase in the polymorphonuclears.

The second case was the one also complicated by a severe Vincent's angina. The gum of the upper jaw was ulcerated so badly that all the incisor and bicuspid teeth either dropped out or were pulled. Two incisors and a bicuspid of the lower jaw were also picked out.

TABLE XV.—BLOOD EXAMINATION OF PATIENT WITH CONVULSIONS AND VINCENT'S ANGINA

No.	Date.	Name of Patient.	Age, Yrs.	Leucocytes.	Lymphocytes. Small.	Lymphocytes. Large.	Transitionals.	Polymorphonuclears.	Eosinophiles.	Mast Cells.
22	10/17	Cath. H...	2	28,500	75.47	9.54	.68	12.5	1.81	.0
	10/24			49,600	70.64	10.41	1.87	15.83	1.25	.0
	10/26			47,500	48.69	15.79	1.31	32.89	1.31	.0
	10/28	(Convulsions)		65,000	50	7.69	.76	39.24	1.92	.38

All examinations were made in the paroxysmal stage. As one would expect in the presence of a necrotic condition, the leucocytes kept on steadily increasing, with a relative decrease in the lymphocytes and an absolute increase in the polymorphonuclears. The case, however, was progressing quite favorably under applications of formalin and a 5 per cent. solution of copper sulphate when, without warning, the child was seized with a minor convulsion. At first it responded quite promptly to treatment, but soon fell into a deep coma. Lumbar puncture was performed for a diagnostic purpose to ascertain the presence of cerebral abscess or a meningitis on account of the ulcerous necrotic condition in the mouth. The result was negative. The clear fluid flowed quite freely and 15 c.c. were removed, following which the patient's breathing was much easier and more regular. The convulsions had a unilateral tendency, especially affecting the left side. Ten hours later the patient died. Autopsy was performed shortly afterward. There was no extracerebral hemorrhage. Dr. William G. Spiller very kindly sectioned and examined the brain for me. He reports:

The right parietal and occipital lobes and the left occipital lobe are greatly congested, but no hemorrhages are found in the cortex or white matter.

Microscopic Examination: The pia of the left paracentral lobule is not thickened, but shows a considerable degree of round-cell infiltration, especially in the fissures. The vessels of the pia and of the cortex are much distended with blood, and those of the latter present a slight perivascular round-cell infiltration. The congestion of the vessels in the right paracentral lobule is about as intense as in the left paracentral lobule, but the round-cell infiltration of the pia is not so distinct.

The optic nerves and chiasm are full of holes, as though many nerve fibers had degenerated and dropped out. The pia of the optic nerve shows some round cell infiltration. A slight round-cell infiltration is found also in the pia of the medulla oblongata. The vessels of the medulla oblongata are distended with blood but not so much as those in the cerebral cortex.

The round cells are such as are often found in meningitis, consisting of small cells with a single nucleus.

The condition is one of moderate meningoencephalitis.

The last blood count was taken during the height of the convulsions and shows nothing more than a higher leucocytosis.

Impetigo Contagiosa

The lesions developed in the period of marked improvement. A slightly increased leucocytosis with an absolute increased percentage of polymorphonuclears and a slight eosinophilia toward the end will be noted.

TABLE XVI.—BLOOD EXAMINATION OF PATIENT WITH IMPETIGO CONTAGIOSA

No.	Date.	Name of Patient.	Age. Yrs.	Leucocytes.	Lymphocytes. Small.	Lymphocytes. Large.	Transitionals.	Polymorphonuclears.	Eosinophiles.	Mast Cells.
13	9/7	Francis ...	1½	15,100	32.07	13.2	2.61	48.69	2.64	.75
	9/5			17,000	28.5	6	2	67.7	5.4	.3

Ecthyma

The lesions developed during the paroxysmal stage. The last count was taken in the period of marked improvement. Changes similar, but more marked, to those found in the case of impetigo will be noted, as one would expect, in the presence of a more severe pustular infection.

TABLE XVII.—BLOOD EXAMINATION OF PATIENT WITH ECTHYMA

No.	Date.	Name of Patient.	Age. Yrs.	Leucocytes.	Lymphocytes. Small.	Lymphocytes. Large.	Transitionals.	Polymorphonuclears.	Eosinophiles.	Mast Cells.
20	8/16	Chas. L....	2	28,900	59.56	5.31	1.46	32.25	1.31	.09
	8/20			30,000	46.5	4.6	.9	44.23	3.7	.06
	9/25			14,500	38.26	5.21	1.3	47.42	6.51	1.3

DIAGNOSTIC VALUE

Each will have to decide this question more or less for himself from the various reports available. Certain it is that there is present in whooping-cough a leucocytosis and an absolute as well as a relative lymphocytosis. When I began this work I was quite skeptical as to its practical value, but gradually was convinced of its worth. It requires a careful examination with a counting of a large number of leucocytes and due consideration of the child's age. In two cases, Nos. 3 and 22, examined early in the catarrhal stage, there was no lymphocytosis and a negative diagnosis was made. These cases afterward proved to be genuine whooping-cough. In a few instances provisional diagnoses were made, but in each case a second examination cleared up the doubt either in a positive or negative way. Unfortunately the busy practitioner may have no opportunity for an examination that takes considerable time. Yet I believe that it will pay to take time, especially if the practitioner

is connected with institutions, hospitals and dispensaries where the disease is rapidly spread. The differential count is of more importance than the leucocyte estimation. The numbers of leucocytes vary a great deal in different cases, and the best methods of counting are still far from being accurate and absolutely reliable. I do not wish to underrate the value of a leucocyte count in conjunction with a differential count, but of the two the latter is of more importance and, I believe, of great interest and much value in aiding an early diagnosis of pertussis.

I wish to express my thanks to Drs. S. McC. Hamill, John M. Cruice and Charles Fife for their kind interest and to the Sisters of Charity, who by their unvarying courtesy and aid made the work both possible and pleasant.

St. Agnes' Hospital.

BOOK REVIEW

DISEASES OF THE HEART. By Prof. Th. von Jürgensen, of Tubingen; Prof. Dr. L. Krehl, of Greifenwald, and Prof. Dr. L. von Schrotter, of Vienna. Edited, with additions, by George Dock, M.D., Professor of Medicine, Tulane University, Medical Department, New Orleans. Octavo of 848 pages, illustrated. Philadelphia and London: W. B. Saunders Company, 1908. Cloth, $5.00 net; half morocco, $6.00 net.

No subject in the whole field of clinical medicine has been so adequately presented in English as that of diseases of the heart. Both in the general text-books on practice, in manuals of physical diagnosis and in special works on the heart, wise teaching, based on thorough anatomical study and sound clinical observation, has been the rule. The translation of a German work on the heart, therefore, must be of unusual excellence, and present the subject from a new standpoint, or with important additions to our knowledge, to justify its acquisition by English-speaking physicians. For it must be admitted that a translation seldom conveys ideas with the clearness and force of the language in which they are originally formulated; also that the delay in publication which it entails necessitates the introduction of the latest work in the form of editorial notes, which break the continuity of the presentation.

The reviewer, already fairly familiar with these monographs in the original, has endeavored to read critically the greater part of the more than eight hundred pages, which the publishers have bound into this single volume, asking himself whether the book justifies its existence in English medical literature. Unfortunately the publishers have made a simple answer to this query impossible. They have bound up in one book five separate monographs: three by von Jürgensen; "Insufficiency (Weakness) of the Heart"; "Endocarditis"; and "Valvular Disease"; Krehl's "Diseases of the Myocardium" and "Nervous Diseases of the Heart"; and "Diseases of the Pericardium," by von Schrötter. The book thus produced is heavy and cumbersome and interposes wholly unnecessary physical obstacles to its enjoyment. Why do American publishers seem to aim at supplying the maximum, and not the minimum, size and weight of product? Much more important, however, is the circumstance that the pure gold of Krehl's learning and experience is mixed with the baser metal of the other contributors, and has to be mined out, as it were, from the inner recesses of this bulky volume. Still, it is worth the effort. No book in English presents the diseases of that fundamentally impor-

tant part of the cardiac mechanism, the heart muscle, except in a cursory manner, as a small supplement to the lesions of the far less important valves. This is, I take it, because the heart has until recently been regarded, in America and England, primarily as subject-matter for the teaching of physical diagnosis. Mackenzie's book marks the beginning of a new epoch of physiologic, as contrasted with anatomic, study, but it is a piece of special pleading. The most striking feature of Krehl's masterpiece is its combination of wide anatomical and physiologic knowledge with ripe clinical experience. His work needs no praise, for it is too well known. Its chief defect, the omission of all the new information about the conducting apparatus of the heart, which has come to light since 1904, has been remedied with discretion by the editor. Among many good chapters, the one on "Cardiac Fear, Cardiac Pain, and Angina Pectoris" seems to the reviewer particularly admirable, and to contain teaching which the American practitioner stands in need of. Methods of treatment in heart disease are set forth with authority and from a valuable section of the book. The note of pessimism, so fatal to therapeutic success, and commonly the result of a deficient experience, is wholly absent. It is of especial interest to see, all through the work, how a wide and accurate knowledge of physiology, and its many unsolved problems, neither interferes with Krehl's practical judgments, nor misleads him into the easy assumption that, because a particular disturbance of function can be imitated experimentally in a particular way, therefore it is explained. Both these object-lessons are called for to-day. It is the difference between the true scientific spirit and a kind of pseudo-science, which thrives especially in medical circles. Krehl, in more than one place, condemns this attitude of mind specifically, as on page 460, when, speaking of the complicated problem of the cardiac rhythm, he says: "We are as yet free from having a clear understanding of the phenomena, and it is our duty openly to acknowledge our ignorance instead of keeping up the state which has been so aptly called by Martius 'sham-physiologism' (*Scheinphysiologismus*), as is done too frequently in this field, especially in the clinical literature." In these days of Emmanuel movements, the American practitioner may also well heed this German professor, when he advises, under the treatment of the cardiac neuroses: "In fact, the physician in these cases often performs the office of the minister, and if he tries to avoid doing so he can never expect to accomplish results."

Of the remaining portions of the volume, the less said the better. Jürgensen's presentation of insufficiency of the heart is involved, full of false assumptions, and much of that *Scheinphysiologismus* against which

Krehl inveighs. He quotes lengthy case reports with obviously erroneous diagnoses in defense of his position; as, for instance, on page 121. This case is so evidently one of interlobular emphysema from rupture of the lung during cough, with consecutive subcutaneous emphysema, that it makes argument from it for a theory of cardiac asthma ridiculous. His discussion of treatment is still worse; pessimistic, valueless as a presentation either of scientific knowledge or clinical experience. His statements as to digitalis, if quoted by any American medical student, would certainly mark him for condition in therapeutics. The discussion of endocarditis is rather better, though not greatly instructive. One gains from it the impression that endocarditis is almost invariably a progressive disease, and that benign rheumatic endocarditis is a myth. His "Valvular Disease" was not worth translating, in view of the available English books like Sansom's and Gibson's. "Diseases of the Pericardium," by von Schrötter, with the editorial emendations, presents the subject in a fairly concise way. All that it gives of value on the important topic of paracentesis of the pericardium is from the hand of the editor.

Throughout the whole volume the wide learning of the editor is in evidence, and he has added much to its usefulness. The translation is satisfactory and errors few. A conspicuous one is on page 728, where "coronary muscles" evidently should read "coronary arteries."

SYSTEMIC BLASTOMYCOSIS

REPORT OF A CASE

BRYCE W. FONTAINE, M.D., MARCUS HAASE, M.D.
AND
ROBERT H. MITCHELL, M.D.
MEMPHIS, TENN.

This case, which we believe to be the first reported from the southern states, occurred in the practice of Dr. Robert H. Mitchell, and was thought to be an unresolved pneumonia.

On Nov. 7, 1908, the forty-second day of the illness, and two days prior to death, Drs. Fontaine and Haase were asked to see the case. At this time the diagnosis of systemic blastomycosis was made from the appearance of the cutaneous lesions, and by demonstrating the organism in the sputum and in the pus.

Patient.—Mrs. H.; aged 27; color white; native of Austria; married; three children; one living. Mother died at 70, cause unknown. Father died in old age, cause and time of death unknown. Patient was one of twelve children, all of whom are dead save one sister. The last sister to die was sick for some time in Austria, with a disease supposed to have been tuberculosis, and was nursed almost solely by our patient.

History.—Shortly after the death of this sister, patient emigrated to this country, coming directly to Memphis. She had been in fairly good health until June 15, 1908, when she began to cough and to lose weight. This condition was regarded as insignificant and was not treated by a physician. On Aug. 1, 1908, the cough became worse, the sputum was increased and slightly blood-stained. In a few days, the sputum became mucopurulent and the patient continued to cough and expectorate until the beginning of her final illness and confinement to bed, which began on Sept. 25, 1908.

Examination.—The patient was first seen by Dr. Mitchell on October 3, one week after the beginning of her final illness, and was admitted to St. Joseph's Hospital the same afternoon, when the following note of her condition was made: Patient markedly prostrated, coughing with expectoration consisting almost entirely of mucus. Temperature 102.3. Respiration 25. Pulse 110. Examination of lungs revealed an area of dulness about two inches in diameter over left upper lobe, over which was heard bronchial breathing and increased vocal resonance. The physical signs were those of an ordinary severe lobar pneumonia, but instead of resolution occurring, the disease progressively increased and finally involved the entire left lung.

Course of Disease.—Throughout the course of the disease the temperature curve was most irregular, varying from 97 to 104 F., the highest and the lowest temperature occurring at any time of the day. The pulse for the first two weeks was quite constant, about 110; later it became very rapid and irregular, reaching 160 several days before death.

Respiration at first showed no marked change from the normal, but on the sixteenth day of the disease it began to be more shallow and frequent, reaching 64 toward the end of the disease.

The urine was examined on October 22, and found normal except for the presence of a few red blood corpuscles. The sputum at first consisted of mucus but on the sixth day of the disease it contained blood of a rusty color. It was tenacious and was expelled with difficulty. Later the sputum became mucopurulent, still being slightly tinged with blood; it was examined on two occasions for tubercle bacilli and was found negative. On the forty-second day of the disease it was found to contain numerous blastomycetes, no examination for that organism having been made prior to that time.

Fig. 1.—Lesions in case of blastomycosis; from photograph taken two days before death of patient.

During the second week of the disease the blood serum responded to the Widal test for typhoid fever.

On October 25, an eruption appeared first on the face, later on the neck, chest, back, legs and thighs in the order named. The first lesion appeared on the forehead as a small papule; on the following day it had increased in size and was capped with a pustule; it continued to enlarge and others appeared over the regions mentioned, until November 7, when the following dermal condition was noted:

Scattered over the body were numerous lesions, about 600 in all, 118 of which were located on the face and head (Fig. 1). The lesions varied in size from a pin-head to a half-dollar; the largest, the one on the forehead, was

oblong in shape, dark red in color, and raised about an eighth of an inch above the surface and covered with a dirty, yellowish crust. On removal of the crust an irregular papillomatous surface was noted, with seropurulent fluid between the papillary projections. The margin of the growth was moderately infiltrated, dark red in color; the mass was soft and mushy to the touch and not painful under mild pressure.

The large lesions on the lip presented a similar papillomatous appearance, were round, smaller, and somewhat more raised above the surface than the one on the forehead; they were not surrounded with dark red, infiltrated areas. All other lesions on the face were raised, round red papules, covered with a yellowish crust, or capped with a pustule, varying in size, the younger or

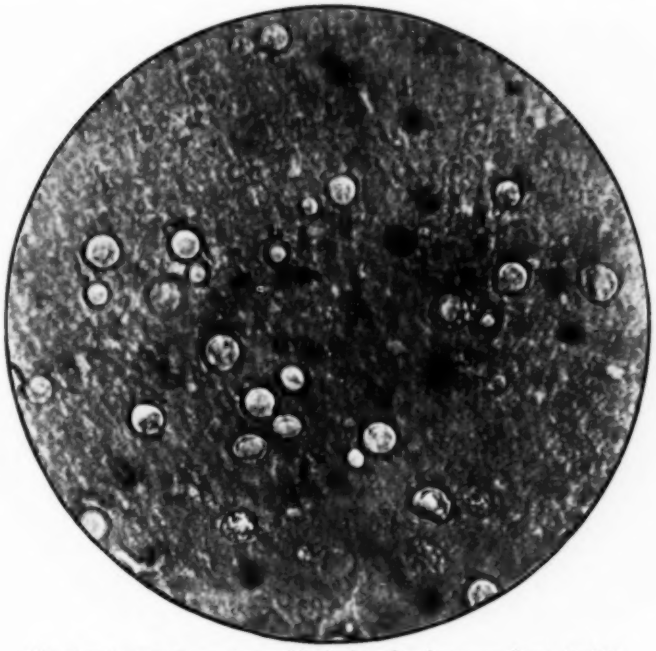


Fig. 2.—Smear of pus from skin lesion showing organism; × 500.

smaller ones being no larger than a pinhead, but all showing, under the crust or pustule, the same papillomatous condition seen in the older larger lesions.

On the anterior portion of the scalp about the median line and one and one-half inches posterior to the border of the hair, among smaller ones, there was one large round lesion over which the hair was matted; it was quite soft and from it there was a constant oozing of seropurulent matter.

On the hands there were numerous lesions, varying in size and shape, the largest being about the size of a twenty-five-cent piece, firm, hard, and surrounded by a dark red, raised, firm border and covered with a dark yellow moderately adherent crust. On removal of the crust the same condition of the surface was noticed as in those on the face.

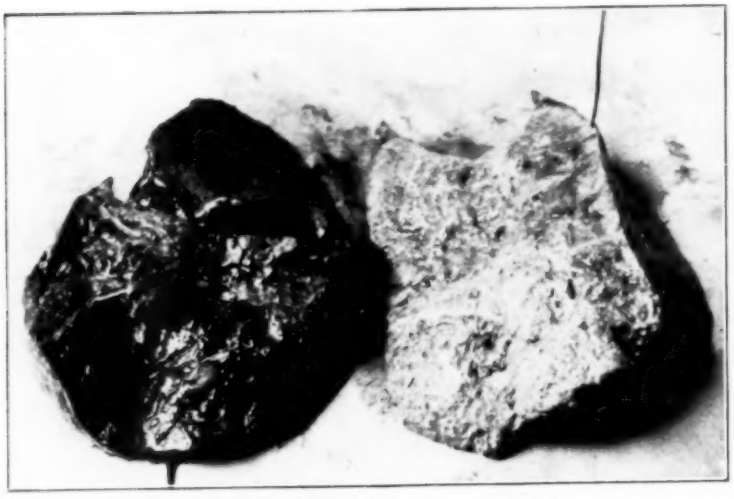


Fig. 3.—Right and left lung sectioned.

Fig. 4.—Spleen after section; note the enormous number of miliary abscesses.

The arms, trunk and thighs presented numerous lesions, none of which was markedly elevated. They showed only a faint pink areola, with little or no induration, differing from the lesions before described, to this extent only. Otherwise they were similar in that they were capped with a crust beneath which was a pustule invariably presenting the irregular surface with small projecting papillæ, from between which the fluid could be pressed.

The patient complained of no pain, burning or itching from the lesions on the skin.

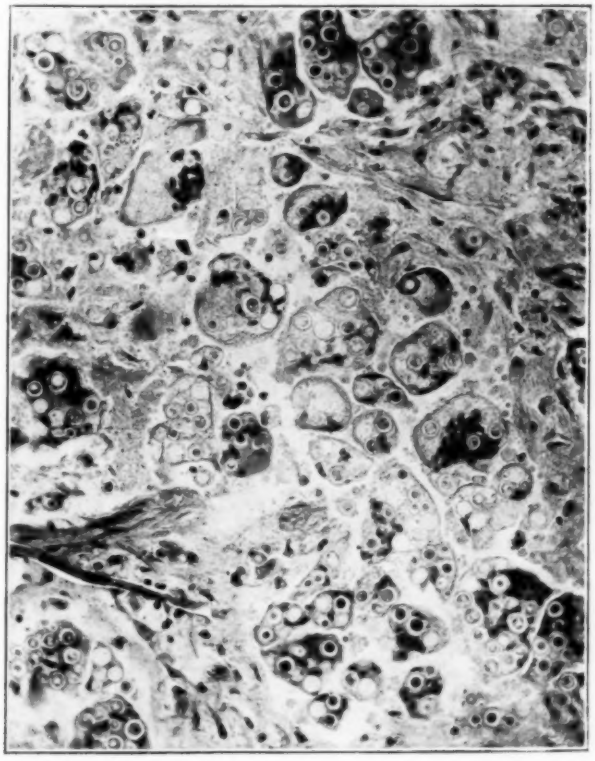


Fig. 5.—Section of lung. × 150; blastomycetes in large syncytial cell masses.

Smears were made from the pus from three lesions and were examined the following morning, without staining; numerous organisms were found, many of them budding (Fig. 2).

None of the lesions was examined microscopically at that time, but at the autopsy three lesions were removed from the face and hands.

The patient was given the usual stimulant and supportive treatment, besides iodin and several doses of pneumococcic serum. Early in the course of the disease moderate doses of potassium iodid were given for several days. No improvement was noted and on November 9, death occurred from toxemia.

AUTOPSY.

This was held two hours after death.

Anatomic Diagnosis:—Pericardial effusion. Catarrhal pneumonia, with miliary and conglomerate abscesses of right lung. Pleuritic adhesions. Catarrhal pneumonia of lower lobe. Necrosis of middle and upper lobes, with miliary and conglomerate abscesses of left lung. Parenchymatous and fatty degeneration with acute congestion of the liver. Parenchymatous degeneration of the kidneys. Acute splenitis, with miliary and confluent abscesses.

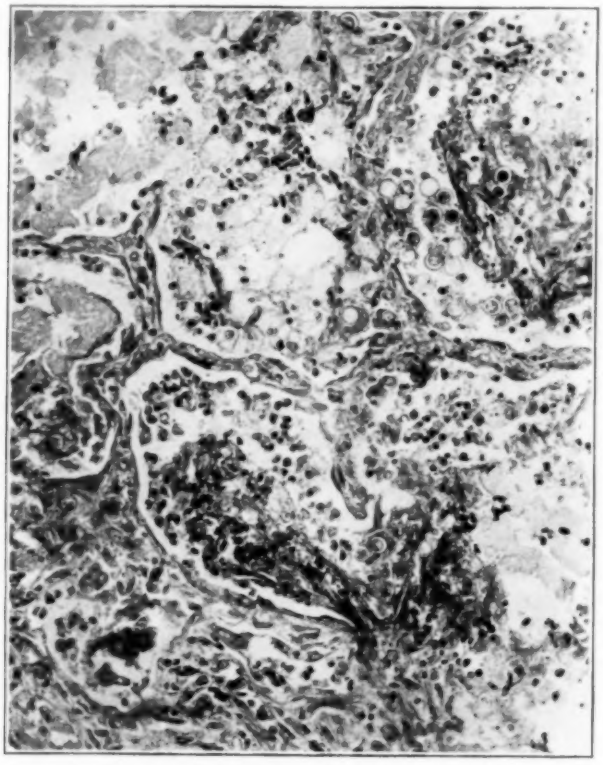


Fig. 6.—Section of lung, × 150; blastomycetes with connective tissue formation and exudation.

Macroscopic Examination.—Body of an emaciated woman about five feet two inches in length, weighing about one hundred pounds. Numerous papules, tubercles, pustules and ulcers were scattered over face, hands, chest, abdomen, back and thighs. The lymphatic glands and visible mucous membranes were not involved.

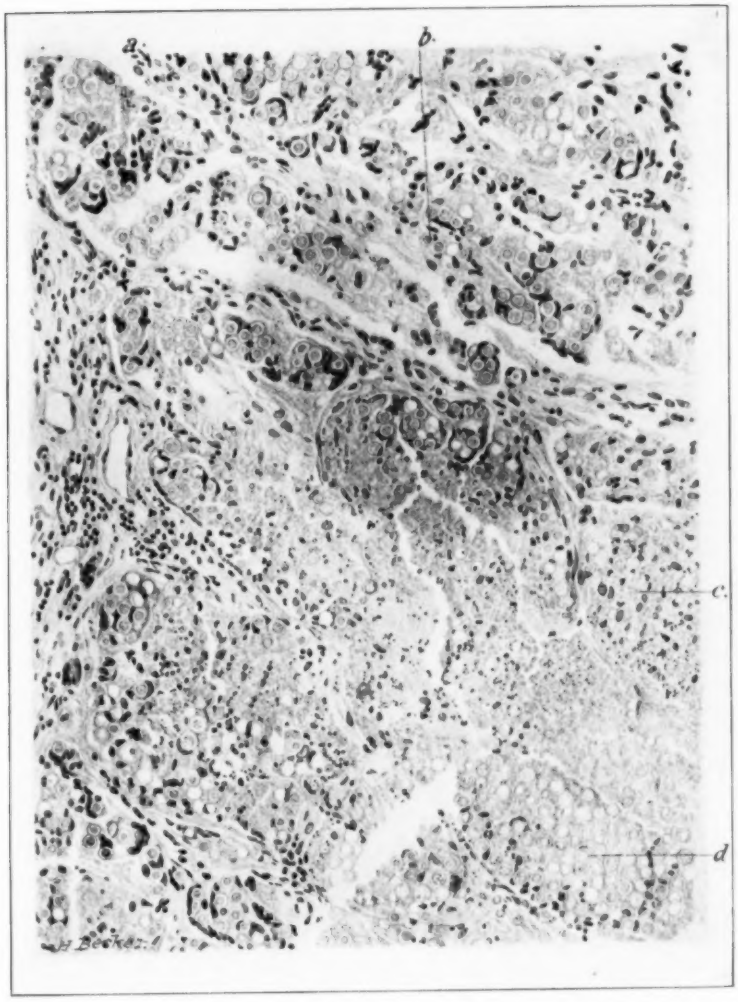


Fig. 7.—Section of lung. × 225; a, wall of alveolus; b, blastomycetes in tissue; c, exudate in alveoli; d, enormous accumulation of blastomycetes in exudate.

Thorax: Pericardial sac contained about six ounces of a clear, straw-colored fluid. Heart normal in size, muscles pale and soft, cavities small. Valve leaflets normal and competent. Valve orifices normal in size.

Lungs: Left visceral and parietal pleura were united throughout by adhesions which were separated with some difficulty, they were so dense at lung. The lung was distended and heavy. Lower lobe solid and of the consistency of liver. Middle and upper lobes were soft and boggy. The three lobes were densely adherent to each other. The surface was rough and covered

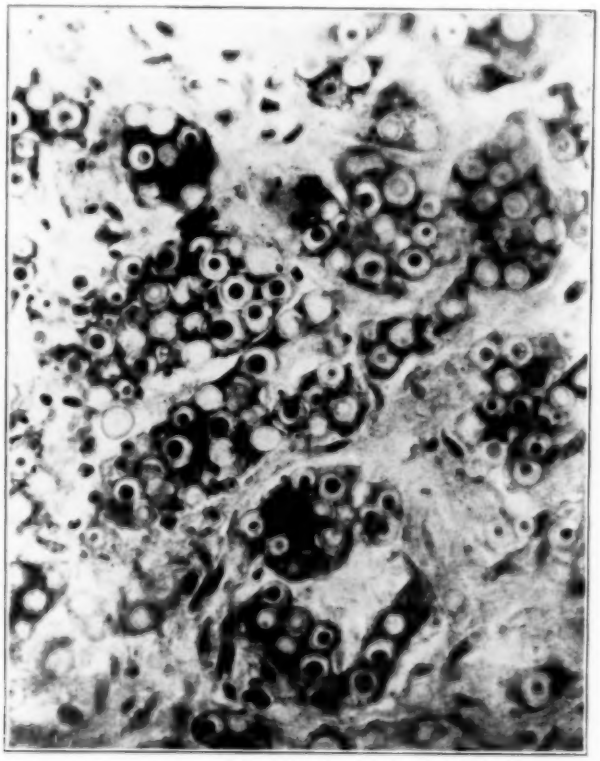


Fig. 8.—Section of lung, × 500; large masses of blastomycetes.

by fibrinous adhesions of a dirty grayish color, mottled with numerous areas varying in size from 1 to 10 millimeters, which were of a yellow color, soft and slightly elevated above the surface of the lung; they were not unlike miliary and conglomerate tubercles. On section of the lung the cut surface was of a dirty grayish color and exuded a thick purulent fluid (Fig. 3). The upper and middle lobes consisted mainly of confluent areas of soft, cheesy, necrotic material, separated by a small amount of bluish-gray lung tissue. The lower lobe contained more lung tissue with a few discrete, grayish-white, soft areas

which had the appearance of beginning necrosis. The bronchi contained a small amount of mucopurulent fluid. Right pleural cavity empty. Right lung distended and heavier than normal; surface smooth and glistening. Posterior part of lower lobe solid, dark red in color, and devoid of air; remainder of lung of a bluish-pink color, semisolid and partly crepitant. Over the entire surface of lung were seen grayish, slightly elevated, discrete areas, irregular in shape and varying from 1 to 10 millimeters in diameter. Lobes not adherent to each other. On section, the surface had a bluish-pink color, was studded with soft yellow areas, irregular in shape, and sharply outlined from the surrounding tissues and evidently areas of necrosis. The surface exuded a bloody air-mixed serum. The bronchi contained some mucopurulent fluid. Smears made from the exudate of both lungs showed blastomycetes in great numbers.

Spleen: Enlarged, measuring 20 by 12 by 10 centimeters. Soft in consistency, dark red in color, and thickly studded with yellow, slightly elevated areas of

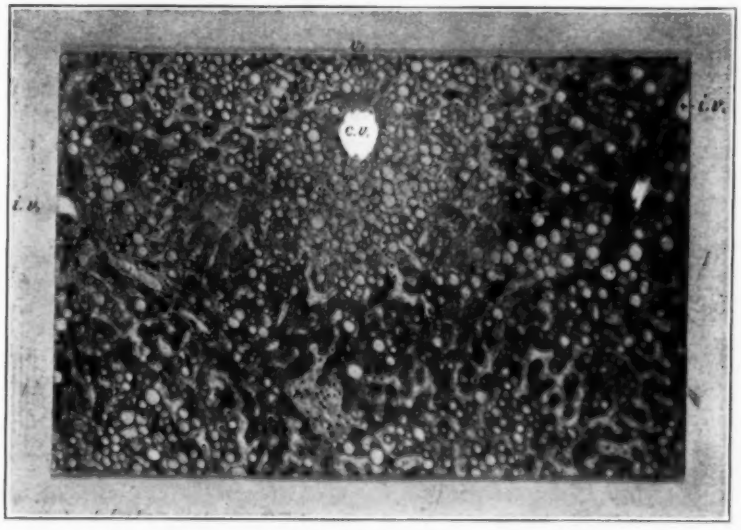


Fig. 9.—Section of liver, × 120: c. v., central vein; i. v., interlobar vessels; liver; v. vacuole in cells.

irregular shape, varying in size from 1 to 10 millimeters. Surface smooth; capsule not thickened. On section, the splenic pulp was found to be dark red in color, interspersed with soft purulent areas of a lemon yellow color, which occupied fully one-third of the organ (Fig. 4). Smears from purulent areas showed numerous blastomycetes.

Liver: Very much enlarged and soft; surface smooth and pale red in color; capsule not thickened. Cut surface pale and greasy. Lobules indistinct; venules distended. No necrotic areas could be seen. Gall bladder empty; ducts free.

Kidneys: Enlarged, pale red in color; capsule easily stripped, leaving a smooth surface. Cortex and medulla increased in thickness. Glomeruli and

tufts not easily distinguished. Venules slightly distended. The kidneys presented the appearance of parenchymatous degeneration and did not contain areas of blastomycotic involvement.

Stomach, intestines, peritoneum, pancreas, uterus and bladder normal.

The brain and cord were not examined.

Microscopic Examination.—Lungs: Under low magnification there was seen a very chronic process in which there was a marked increase of fibrous con-

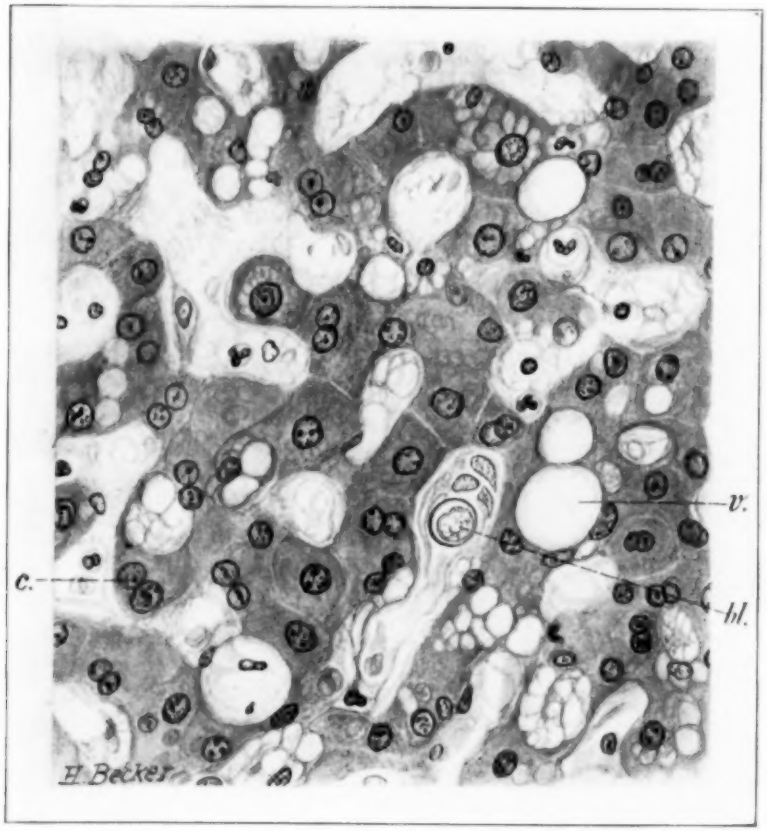


Fig. 10.—Section of liver. × 575; c., liver cells; v., vacuole; bl., blastomyces (the only one found in section).

nective tissue in the alveolar walls and about the blood vessels. In places, the infiltration was so dense that it almost replaced the lung structure. Throughout the fibrous tissue could be seen areas of necrosis, and near these necrotic areas could be seen groups of syncytial cells containing blastomycetes (Fig. 5).

The more acute process consisted of a pneumonia in which most of the alveoli were seen packed with exudation. Under higher magnification the chronic process could be seen infiltrated with round cells of the lymphoid type. Under high magnification, there could be seen slight congestion of the vessels, fibrous infiltration of the alveolar walls and about the blood vessels. The epithelial cells lining the alveoli were swollen and degenerated. In the alveoli the exudation was seen to consist of red blood corpuscles and blastomycetes lying free, polymorphonuclear leucocytes, epithelial cells in process of degeneration and

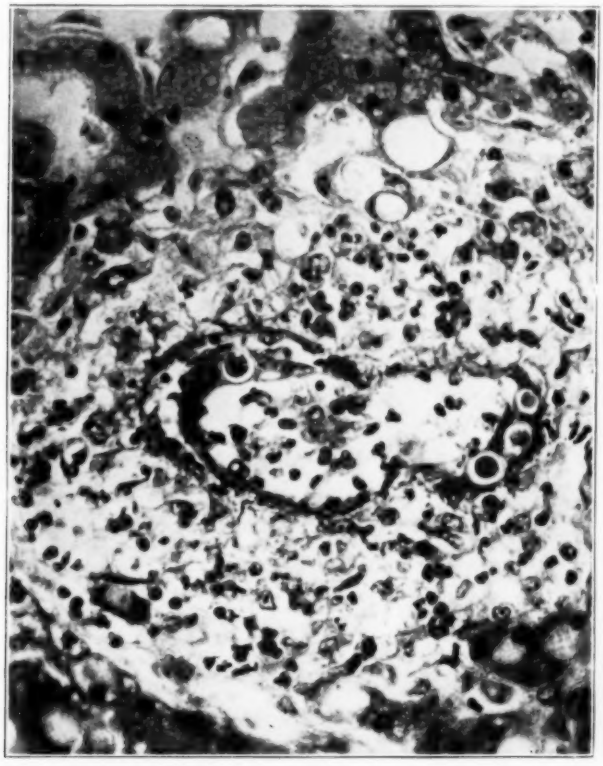


Fig. 11.—Liver; small nodule with organisms in the endothelium.

threads of fibrin (Figs. 6 and 7). The bronchi had thickened walls in which there could be seen a few blastomycetes, the lumen containing a slight exudate. The lesions in the lungs were remarkable for the extreme fibrosis, the large number of syncytial cells, and the enormous number of blastomycetes. (Fig. 8). Most of the lesions were extremely chronic, but there had been a very acute extension which occurred by way of the bronchi.

Liver: Section showed dilatation of the intralobular vein, containing a few blood corpuscles, surrounded by an extreme grade of fatty degeneration which

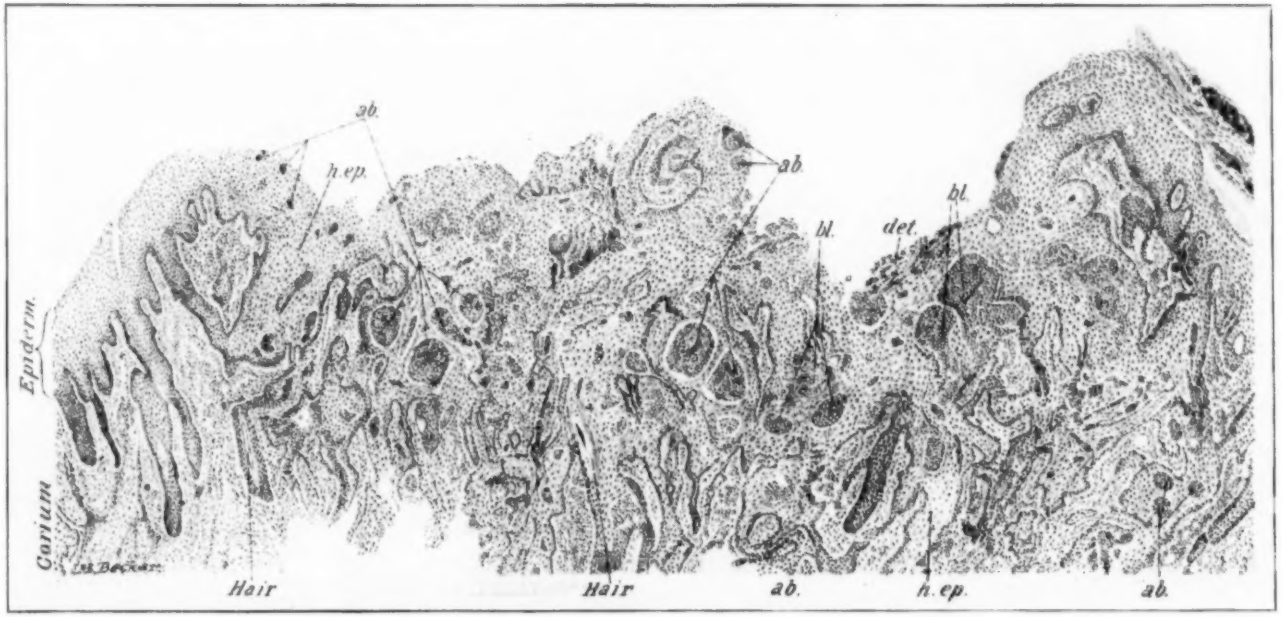


Fig. 12.—Section of skin (blastomycosis), 40 times enlarged: h. ep., hypertrophied epithelium; ab., miliary abscesses; bl., accumulations of blastomyces; det., detritus.

extended almost to the periphery of the lobule (Fig. 9). The liver cells in the periphery and about the portal area were slightly degenerated and were separated by a few round cells of the lymphoid type. The vessels about the periphery of the lobule were of normal size (Fig. 10). There were about the intralobular veins a few nodules of blastomycotic infiltration. In the endothelium of the veins there could be seen a few blastomycetes (Fig 11).

Spleen: Malpighian follicles were of normal size and contained areas of hyaline degeneration. There was also slight hyaline infiltration in the intima of the blood vessels and marked proliferation of the cells normally present. There could be seen slight diffuse fibrosis with extravasation of blood throughout the

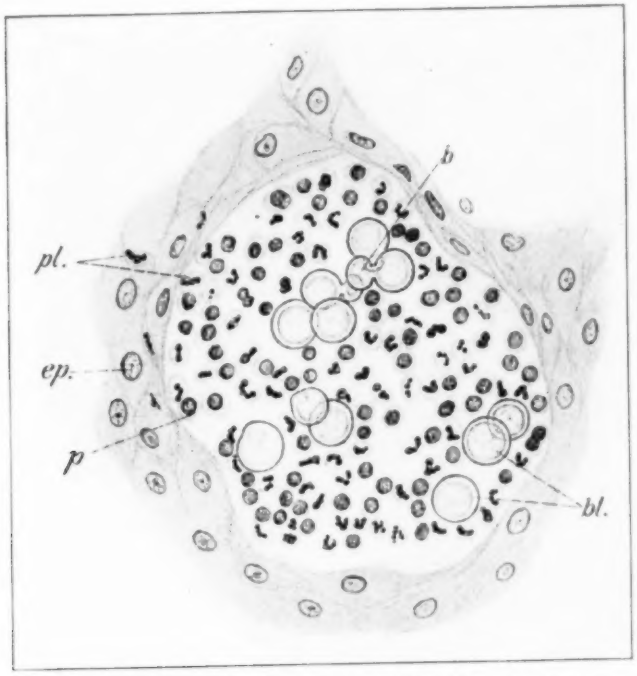


Fig. 13.—Abscess in epidermis: ep., epithelial cell.; bl., blastomyces; b., budding blastomyces; pl., leucocytes; p., lymphoid cells.

parenchyma. Scattered through the parenchyma were seen miliary abscesses: around the abscesses was a slight attempt at encapsulation. The center of abscesses was in a condition of liquefaction necrosis and contained numerous blastomycetes.

Kidneys: Epithelial cells lining the uriniferous tubules were swollen and fragmented; and the nuclei were obscured. The cells contained granular matter and in many places were desquamating. The glomeruli were normal in appearance.

Skin: Under low magnification. Beginning from without, there was an absence of the corneous layer and the transitional layers beneath; the prickle layer was markedly hypertrophied and the cells edematous, taking the stain poorly. Throughout the epidermis small abscesses could be seen. The basal layer, owing to the hypertrophy, was pushed far into the corium but in all instances could be seen intact. The corium showed areas of intense infiltration

Fig. 14.—Skin; b., budding blastomyces; 575 times enlarged.

with numerous microscopic abscesses, and even under the low magnification, blastomycetes could be seen (Fig. 12).

Under high magnification the infiltration was seen to consist largely of round cells instead of the usual plasma cells found in other cases of blastomycosis. A few such cells were found only after repeated search. We were unable to demonstrate any giant cells. The contents of the abscesses were small round

Fig. 15.—Epidermis; minute abscess started by a parasite in epithelium; × 575; bl., blastomyces; l., leucocyte.

cells of the lymphoid type, leucocytes, nuclear fragments and numerous organisms (Fig. 13). The abscess walls were composed of apparently normal connective tissue fibers with flattened compressed connective tissue cells. The abscesses were started by the blastomycetes establishing themselves between the epithelial cells, followed by the emigration of polymorphonuclear and lymphoid

cells (Figs. 14 and 15). Numerous sinuses filled with organisms could be seen in the epidermis and corium between the abscesses (Fig. 16).

The histopathology of the skin in our case differed from that in those previously reported in that we found only a few plasma cells, no giant cells and great numbers of organisms. The organisms in all the lesions were seen to multiply only by budding, and in the sections from the skin and lungs could be seen buds in various stages of development (Figs. 14, 15 and 17).

The first case of systemic blastomycosis was described by Busse-Buschke in 1894, and there have been reported some twenty-three cases.

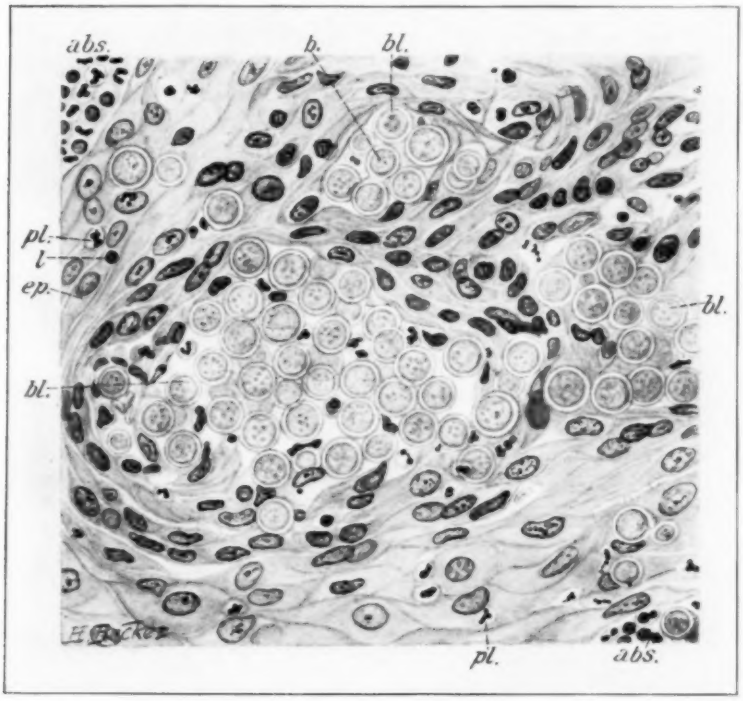


Fig. 16.—Blastomyces in a sinus of papilla (skin), enlarged 575 times; ep., epithelial cell; pl., polynuclear leucocyte; bl., blastomyces; b., budding blastomyces; l., lymphoid cell; abs., abscess.

A majority of the cases are reported from Chicago, and the most important work on the subject has come from that city. A great number of the cases reported are in foreigners, and it undoubtedly exists in every large city among immigrants.

The organisms which are the causative factor of the disease, the blastomycetes, are vegetable micro-organisms belonging to the yeasts or sprouting fungi. They are oval or round bodies, varying in size from 8 to 12 micromillimeters. They have a doubly contoured capsule, a protoplasm which is finely granular and often vacuolated. Between the

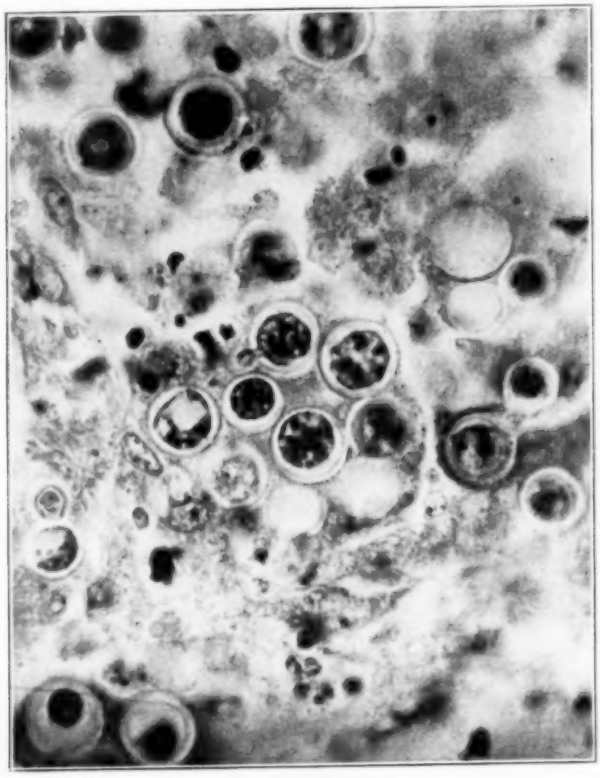


FIG. 17.—Section of lung, × 1,000; organisms, showing budding.

protoplasm and the capsule a clear zone of varying thickness can be seen. The protoplasm is often nearer the capsule at one pole than at the opposite, and the clear space varies correspondingly in size.

Reproduction occurs in living tissue by budding and in cultures by mycelial formations.

According to Montgomery and Ormsby, the male sex has furnished a majority of the cases, there being nineteen males to four females among the cases reported in their exhaustive articles.[1]

Inasmuch as the lungs were so often primarily affected (in 65 per cent. of the cases reported), it is important to consider the respiratory tract as a mode of entrance for the parasite. We are quite sure that the disease existed in the lungs in our case for some months before the final illness, and it is more than probable that the illness from which the patient's sister died was the same disease. It is easy to confound the disease with tuberculosis. Clinically, the two diseases of the lungs can hardly be distinguished, except by a microscopical examination of the sputum. The gross and microscopic appearance of the lesions are remarkably like those of tuberculosis.

Of interest is the fact that the serum from this case responded to the Widal test for typhoid fever, and this is in keeping with the observation of Collins, in which it was found that repeated inoculation of rabbits or goats with brewer's yeast led to the production of agglutinins for the typhoid bacillus and other organisms of the dysentery class.

The disease never occurs without cutaneous or subcutaneous lesions. The skin lesions are usually secondary, and are metastases from the visceral lesions.

The organism can nearly always be demonstrated in the sputum or in the pus from the cutaneous lesions by treating a smear with a 1 per cent. solution of potassium hydrate.

In our case enormous numbers of blastomycetes were demonstrated in the sputum and in the pus from the cutaneous lesions.

We regret that we did not have time to attempt treatment with a vaccine.

We are very grateful to Drs. Gilchrist, of Baltimore, and Councilman and Pratt, of Boston, for many helpful suggestions in the study of the case.

---

1. Montgomery, F. H., and Ormsby, O. S.: Systemic Blastomycosis, THE ARCHIVES INT. MED., 1908, ii, 1.

GLANDULAR FEVER

REPORT OF AN EPIDEMIC IN THE CHILDREN'S WARD OF THE UNION PROTESTANT INFIRMARY

J. EDWARD BURNS, M.D.
BALTIMORE

Glandular fever, an acute infectious disease principally affecting the cervical glands, was first described by Pfeiffer in 1889. Since that time various writers, West, Korsakoff, Gourichon, Terflinger and others, have reported epidemics and written extensively about it, but conclusions as to its etiology, the portal of entry of the organism causing the infection, the extent of the infection, and the complications arising therefrom are very diverse.

The cases reported in this article are nine in number. The first six occurred in children from 2½ to 5 years of age. The last three occurred in the family of Patient 6 after she had left the hospital, and, although not seen in the acute stage, are reported because the clinical history corresponded precisely to that in the cases observed. In this family epidemic only adults were affected. West reported an epidemic of 96 cases occurring in children and Terflinger one of 150 cases occurring in adults, thus showing that this disease, although considered one of childhood, may affect individuals at most any age.

The cases reported occurred in the months of February and March, and made their first appearance two months after the children's ward had been isolated on account of the measles, scarlet fever and diphtheria in the city. The first case began on February 15, the second on the 16th, the next two on the 17th, and the last two on the 18th.

The first case in the family of Patient 6 developed twenty-four hours after the child had reached home. Her mother was the first member of the family affected; none of the family had seen the child for two and a half months previously. From this one would conclude that the incubation period could be as short as twenty-four hours, although most writers think it from seven to nine days.

All the cases showed a leucocytosis from 18,800 to 26,400 during the disease. The variations in the differential count during the disease were as follows:

	Per Cent.
Polymorphonuclear leucocytes	37 to 74
Small mononuclears	20 to 50
Large mononuclears	2 to 11
Eosinophiles	0.5 to 5
Transitionals	1 to 7
Mast-cells	0.5

The small mononuclear elements of the blood seem to be the ones principally increased. The coexistence of tuberculous, gonorrheal and chickenpox infections in some of the cases makes the blood picture somewhat confusing.

Cases 1 and 2 showed a marked leucocytosis according to the absolute count, yet the differential counts were normal. These latter must have been due to an uneven distribution of leucocytes, for it seems very unusual to suppose that all the leucocytic elements of the blood could have been proportionately increased.

Leucocytes after convalescence varied from 5,000 to 8,000.

The variations in differential count after convalescence were as follows:

	Per Cent.
Polymorphonuclear leucocytes	13 to 54
Small mononuclears	30 to 70
Large mononuclears	2 to 14
Eosinophiles	1.4 to 13
Transitionals	1 to 6.5
Mast-cells	0.5 to 2.5

After convalescence there seems to be a still greater relative increase in the small mononuclear elements of the blood.

Throats and tonsils of all the patients were injected, but showed no exudate, and the cultures made showed *Staphylococcus aureus*.

CASE 1.—The patient, R. H., was sent in for treatment of paralysis of left leg due to anterior poliomyelitis. Swelling of glands of both sides of neck was first noted on February 15. At this time his temperature was 101.8, pulse 124. The patient complained of tenderness of cervical glands, stiffness of neck, thirst and loss of appetite. Enlargement of glands was not confined to the cervical group, of which the upper ones, anterior and posterior to the sternomastoid, were chiefly affected, but the axillary and inguinal groups were also enlarged, although to a much less extent. The cervical glands were the only ones tender, and this lasted only three days, after which the swelling began to decrease. No abdominal pain or tenderness present. The patient was constipated. Pharynx and tonsils injected, but no exudate present. Throat culture showed *Staphylococcus aureus*. On February 16 the white blood count was 26,400. The differential count was as follows:

	Per Cent.
Polymorphonuclear leucocytes	74
Small mononuclears	22
Large mononuclears	2
Eosinophiles	0.5
Transitionals	1

On February 20 the differential count was:

	Per Cent.
Polymorphonuclear leucocytes	65
Small mononuclears	20
Large mononuclears	6
Eosinophiles	5
Transitionals	3

Urinary examination showed absolutely no signs of nephritis. The patient left the hospital March 9 before the swelling of glands had entirely disappeared.

CASE 2.—F. R., male, aged 2½ years, epileptic, had swelling of cervical glands of both sides first noted on February 16. On February 15 the temperature rose to 100.6 and on the 16th to 101.6 and then gradually declined.

On February 17 the patient's neck was painful and stiff. The soreness lasted one day. After this the glands began to decrease in size, but those on the left are still somewhat enlarged. Axillary and inguinal glands not involved. Pharynx and tonsils injected, the latter enlarged, but showed no exudate. Throat culture showed *Staphylococcus aureus*. No abdominal pain or tenderness. The patient is habitually constipated. There was loss of appetite.

On February 16 the white blood count was 22,100. The differential count was as follows:

	Per Cent.
Polymorphonuclear leucocytes	63.5
Small mononuclears	30
Large mononuclears	2
Eosinophiles	1
Transitionals	2.5
Mast-cells	0.5

On February 20 the differential count was as follows:

	Per Cent.
Polymorphonuclear leucocytes	66
Small mononuclears	25
Large mononuclears	5
Eosinophiles	1
Transitionals	2

The patient is still in the hospital and doing apparently as well as before the attack of glandular fever.

CASE 3.—E. McD., male, aged 3½, had Pott's disease (high dorsal); swelling of cervical glands of both sides first noticed on Feb. 17. Axillary and inguinal glands not involved. No rise of temperature. Swelling and tenderness of glands, and stiffness of neck lasted until February 20, after which time the tenderness and stiffness disappeared, and the swelling gradually decreased. The patient held his hands to his ears as if suffering with earache. No abdominal pain nor tenderness. The patient was not constipated; had no sore throat. He had loss of appetite; has had swelling of glands of neck three times previously.

On February 20 the red blood count was 4,200,000; white blood count, 21,800; differential count, as follows:

	Per Cent.
Polymorphonuclear leucocytes	44
Small mononuclears	43
Large mononuclears	6
Eosinophiles	3
Transitionals	3
Mast-cells	0.5

On March 27 the leucocyte count was about 6,500; the differential count, as follows:

	Per Cent.
Polymorphonuclear leucocytes	44
Small mononuclears	49
Large mononuclears	5.3
Eosinophiles	1.4

The patient is still in hospital and general condition seems about the same as before he had glandular fever.

CASE 4.—P. K., male, aged 5, had tuberculosis of hip (left) and lumbar kyphosis; swelling of cervical glands of both sides first seen on February 17. Axillary and inguinal groups not involved. No tenderness of cervical glands. Some stiffness of neck. Swelling increased until February 20 and then began to subside. On February 17 the temperature rose to 100 and on the 21st to 100.1. It then gradually fell to normal. The pulse showed no peculiarities. No abdominal pain nor tenderness. Pharynx and tonsils somewhat injected but patient complained of no sore throat. No exudate present. Throat culture showed *Staphylococcus aureus*. The patient was not constipated.

On February 20 the differential count was as follows:

	Per Cent.
Polymorphonuclear leucocytes	48
Small mononuclears	38
Large mononuclears	9.5
Eosinophiles	3
Transitionals	3.3

On March 27 the leucocytes were about 5,000; the differential count was as follows:

	Per Cent.
Polymorphonuclear leucocytes	27
Small mononuclears	49
Large mononuclears	6.8
Eosinophiles	13
Mast-cells	2.5
Transitionals	1

The patient is doing well. Cervical glands still somewhat enlarged.

CASE 5.—M. H., female, aged 5, had tuberculosis of hip (left) and chickenpox; bilateral swelling of cervical glands first noted on February 18; no other glandular involvement. On this day the temperature rose to 100.8, pulse to 120. The temperature gradually fell to normal by February 23, by which time the tenderness of glands and stiffness of neck had disappeared, and swelling of glands was beginning to decrease. The patient complained of earache. Pharynx and tonsils injected, but no exudate present. Throat culture showed *Staphylococcus aureus*. The patient lost her appetite and was constipated. No abdominal pain or tenderness.

On February 20 the white blood count was 18,800; the differential count was as follows:

	Per Cent.
Polymorphonuclear leucocytes	37
Small mononuclears	50
Large mononuclears	10
Eosinophiles	2.2
Transitionals	2

On March 27 absolute leucocyte count was about 5,000; the differential count was as follows:

	Per Cent.
Polymorphonuclear leucocytes	27
Small mononuclears	59
Large mononuclears	6
Eosinophiles	2.5
Mast-cells	0.5
Transitionals	4

The patient is doing well. She has entirely recovered from both her chickenpox and glandular fever without any ill effects.

Case 6.—*N. S.*, female, aged 3, had gonorrheal arthritis of hip (left). On December 29 patient developed tonsillitis; on January 27 left tympanic membrane ruptured due to purulent otitis media; on January 30 patient first showed signs of chickenpox, and on February 18 swelling of cervical glands (left side) was first noted. On February 19 the patient's temperature rose to 101.6, pulse to 144. Cervical glands were tender and neck stiff. Axillary and inguinal glands also somewhat enlarged. By February 23 tenderness of glands had disappeared and swelling was beginning to decrease. At onset pharynx and tonsils were injected. Latter were also enlarged. Throat culture showed *Staphylococcus aureus*. There was no abdominal pain or tenderness. Bowels were regular. On February 20 the differential count was as follows:

	Per Cent.
Polymorphonuclear leucocytes	42
Small mononuclears	40
Large mononuclears	11
Transitionals	7
Mast-cells	0.5

Patient left the hospital on February 28 with cervical glands still somewhat enlarged.

On March 23 I was told by Dr. W. S. Baer, orthopedist to the Johns Hopkins Hospital, that he had heard that several members of the family of Patient 6, who is a patient of his, had glandular fever. Through the kindness of their family physician, Dr. William T. Watson, I was permitted to see them. On arriving at their home I found that three members of the family had had what clinically seemed to be glandular fever. The last patient had recovered two days previously, but all showed some enlargement of the cervical glands still. Throat cultures and blood smears were taken from all three and from Patient 6. Culture from the latter showed *Staphylococcus aureus* as before, and differential count was as follows:

	Per Cent.
Polymorphonuclear leucocytes	13
Small mononuclear leucocytes	70
Large mononuclear leucocytes	14
Eosinophiles	0.5
Transitionals	3

The leucocyte count was about 7,500; and the cervical glands were still slightly enlarged.

Case 7.—The patient, the mother of Patient 6, aged 25, was apparently a healthy woman; she had not seen her daughter for two and a half months and had been perfectly well until the latter's return home on February 28.

On the evening of March 1 the patient says she felt tired and ached all over, and on the morning of March 2 both sides of her neck were swollen and painful. Her neck was stiff, throat very sore; she had a headache, and ached all over. She

was very thirsty, had no appetite, and was constipated. The neck was swollen and painful for one week, after which time it began to subside. At the onset the patient was nauseated and vomited. No abdominal pain nor tenderness.

On March 23 leucocytes were about 5,000; the differential count was as follows:

	Per Cent.
Polymorphonuclear leucocytes	49
Small mononuclears	34
Large mononuclears	4
Eosinophiles	4
Transitionals	6.5
Mast-cells	0.5

Throat cultures showed *Staphylococcus aureus*. Glands of neck still somewhat enlarged.

CASE 8.—The patient, grandmother of Patient 6, aged 50, apparently healthy, on March 13 had headache, ached all over, and had chills. At the same time both sides of neck began to swell and become painful. The neck was stiff and throat very sore. The patient was very thirsty, had no appetite, and was constipated. Swelling and tenderness of glands of neck lasted about one week, after which time it subsided. No abdominal pain or tenderness.

On March 23 the leucocyte count was about 7,500; the differential count was as follows:

	Per Cent.
Polymorphonuclear leucocytes	49
Small mononuclears	41
Large mononuclears	2
Eosinophiles	3.5
Transitionals	4.5

A throat culture showed *Staphylococcus aureus*. Glands of neck still somewhat enlarged.

CASE 9.—Patient, maternal uncle of Patient 6, aged 20. General health good. Bilateral swelling of neck first noticed on March 15. At this time patient had a headache and a feeling of general malaise. The neck was stiff and throat very sore. The patient was thirsty, lost his appetite and was constipated. Swelling and tenderness of neck lasted about one week. No abdominal pain or tenderness.

On March 23 the leucocytes were about 5,000; the differential count was as follows:

	Per Cent.
Polymorphonuclear leucocytes	54
Small mononuclears	30
Large mononuclears	12
Eosinophiles	2
Transitionals	3

Throat culture showed *Staphylococcus aureus*. Axillary and inguinal, as well as cervical glands, still somewhat enlarged.

In the first six cases the enlargement of the cervical glands occurred at the same time on both sides, with the exception of Case 6, and in the last three cases there was a history of simultaneous enlargement of the glands of both sides of the neck. In only one instance, that of Case 6, was there a unilateral involvement. The swelling of the glands seemed to increase on both sides at the same rate, and with the tenderness seemed

to reach a maximum on the third day, after which time the tenderness disappeared and the swelling began to decrease gradually. The upper glands of the chains anterior and posterior to the sternomastoid muscle were the ones chiefly swollen and tender. All the glands involved were hard and discrete. Stiffness of the neck seemed to disappear with the tenderness of the glands and was due most probably to the latter symptom. The axillary and inguinal group were slightly enlarged and hard in two of the cases. None of the cases showed any signs or gave any history of the occurrence of suppuration of the involved glands.

The only definite period of incubation that could be determined with any certainty was that of Case 7, for both the patients in the ward and those on the outside may have become infected at the same time from the same source, or later from other patients. Yet, on account of the varying degrees of individual resistance, the period of incubation would vary greatly. Patient 7 had not seen her child (Patient 6) for two and a half months previously, nor could she remember having been near any one suffering with this disease until she took her child home. This incubation period of twenty-four hours is, as far as I have been able to ascertain, the shortest one recorded.

In all the cases observed there was injection of the pharynx and tonsils, but no exudate was present, and all the outside cases gave a history of an intense pharyngitis. This would seem to indicate the probable location of the portal of entry of the organism causing the infection and the finding of *Staphylococcus aureus* in all the throat cultures might mean that this was the etiologic factor. The chief objection to this latter assumption is that in pyogenic infections the blood usually shows an increase in the polymorphonuclear leucocytes, whereas in this infection, as has been shown above, there is an increase in the small mononuclear elements, both during and after the disease. Cases have been reported in which suppuration occurred and its non-appearance in our cases could not be used as an argument against the pyogenic theory of infection.

A feeling of general malaise with, in some cases, a slight rise of temperature on the day preceding the enlargement of the cervical glands were the first symptoms noted. Later stiffness of the neck, swelling and tenderness of the cervical glands, thirst, loss of appetite, and constipation were the most constant symptoms. Patient 8 had chills at the onset. Nausea and vomiting occurred at onset in Case 7, and this, excepting the constipation which occurred in nearly all the cases, was the only symptom indicating that possibly the disease might be due to an autointoxication from the intestinal tract, as has been thought to be

the case by some writers. None of the patients had any abdominal pain or tenderness.

The pulse showed nothing beyond an increase in rate in some of the cases, the volume tension, force and rhythm being unchanged. The temperature varied from 101.8 F. to normal at the onset, and in cases of a rise fell by lysis. In the case of the tuberculous patients whose temperature curve was not normal the superadded infection made very little, if any, change.

The urine was examined where it was possible and showed absolutely no signs of nephritis, either during or after the disease; in fact, no change in its condition from what it had been previous to the infection was noted.

NOTE.—The following articles may be found of interest on this subject:
Gourichon: Thèse de Paris, 1895.
Arch. Pediat., 1896, xiii, 889.
Jahrb. f. Kinderh., 1889, xxiv, 257.
Arch. f. Kinderh., 1905, xli and xlii.
Ztschr. f. klin. Med., 1907, lxii, 170-178.
Monchau-Beuchant: Pédiatrie prat., 1908, vi, 223-227.
Kühner: Kinder. Arzt, 1908, xix, 121-125.
Werner: Tidsshr. f. d. norske Lægefor., 1908, xxviii, 345-349.
Crane: Ohio Med. Jour., 1908, iv, 143-149.
Terflinger, F. W.: Epidemic of glandular fever. Jour. Am. Med. Assn., 1908, i, 765.
Jones: Amer. Jour. Med. Sc., 1908, sew series, cxxxv, 346-351.

THE ADMINISTRATION OF TUBERCULIN

E. C. L. MILLER, M.D.
From the Research Laboratories of Parke, Davis & Co.
DETROIT

In the early days of tuberculin therapy the administration of large doses proved so disastrous that its use was almost completely abandoned. Now, under the leadership of Goetsch, Sahli, Denys, Spengler, Wright, Trudeau, and others, it is again coming into vogue, but all seem to be agreed that it must be given in small doses. The purpose in giving small doses is to avoid a reaction, which is now recognized as harmful to the patient and as influencing unfavorably the subsequent treatment. Sir A. E. Wright does not pretend to increase his dose systematically, but is content if he can keep the tuberculo-opsonic index of his patient "above normal." Except for Wright, most workers look on the administration of tuberculin as a process of immunization of the patient, and hence as the patient's immunity gradually increases they gradually increase the dose. The dose should increase *pari passu* with the immunity of the patient, but, as there is as yet no practical means of measuring the patient's immunity, treatment at this point becomes difficult. A working compromise is usually effected by laying out for the patient a series of doses progressively increasing in size to be administered at regular intervals, the effect of each dose being watched most closely and the physician holding himself ready to change the series at any point, so as to adapt it more perfectly to the requirements of that particular patient.

To meet the demand for tuberculin in small doses for such cases various manufacturers, both German and American, have put out serial dilutions so that the physician could obtain tuberculin of a strength adapted to each stage of the course of treatment. These dilutions are usually decimal and of the following type:

First dilution,	1 to 1,000,	contains 1	cubic millimeter per c.c.
Second dilution,	1 to 10,000,	contains 0.1	cubic millimeter per cc.
Third dilution,	1 to 100,000	contains 0.01	cubic millimeter per c.c.
Fourth dilution,	1 to 1,000,000,	contains 0.001	cubic millimeter per c.c.

In using this series the physician would give the patient, let us assume, as:

First dose, 0.1 c.c. of the fourth dilution or 1/10,000 cubic millimeter.
Second dose, 0.2 c.c. of the fourth dilution or 2/10,000 cubic millimeter.
Third dose, 0.3 c.c. of the fourth dilution or 3/10,000 cubic millimeter.

And so on up to the tenth dose, 10/10 or 1 c.c. of the fourth dilution, containing 10/10,000 or 1/1,000 cubic millimeter.

This amount (1/1000 cubic millimeter) is also contained in 1/10 c.c. of the third dilution, and hence, to avoid injecting the larger quantities of fluid that would be necessary if the fourth dilution were used for larger doses, a change is made to the third dilution and the series continued as follows:

Tenth dose, 0.1 c.c. of the third dilution or 1/1,000 cubic millimeter.
Eleventh dose, 0.2 c.c. of the third dilution or 2/1,000 cubic millimeter.
Twelfth dose, 0.3 c.c. of the third dilution or 3/1,000 cubic millimeter.

And so on up to the twentieth dose, 10/10 or 1 c.c. of the third dilution, 10/1,000 or 1/100 cubic millimeter, when a change is made to the second dilution and so on.

On the face of it this would seem to be a series that covers the ground nicely from the lowest to the highest desired dose. As a matter of fact, there are objectionable features in this series, which it is the purpose of this paper to point out.

The character of the series is best shown by plotting it as a curve, using the days of treatment for a base line and doses for ordinates. Such a curve is shown in Figure 1, where the numbers on the base line represent days numbered consecutively from the beginning of treatment, and the ordinates represent doses expressed in fractions of a cubic millimeter. Dots on the curve represent injections. It is assumed that an injection is given every five days and that the series is followed as laid out, the curve covering an interval of 100 days and the doses ranging from 1/10,000 to 2/100 cubic millimeters.

The most striking feature of the curve is that it is not uniformly progressive, but is broken up into portions that differ very much from one another. In the first section (A to B) the doses are regularly increased by 1/10,000 cubic millimeter and the total increase is from 0 to 1/1,000 cubic millimeter, the doses being taken from the fourth dilution. When the change is made to the third dilution (plotted as the second section: B to E) the very first increase (from B to C, 1/10 c.c. to 2/10 c.c., 1/1,000 to 2/1,000 cubic millimeters) is 1/1,000 cubic millimeter, or as much of an increase in five days in one jump as had been attained during the previous fifty days and by ten steps. The section continues on by uniform increases of 1/1,000 cubic millimeter up to E, where another change occurs. The whole of the third section could not be plotted for lack of room, but the first step (E to H) is shown, and here again we have a similar jump—the increase from E to H (1/100

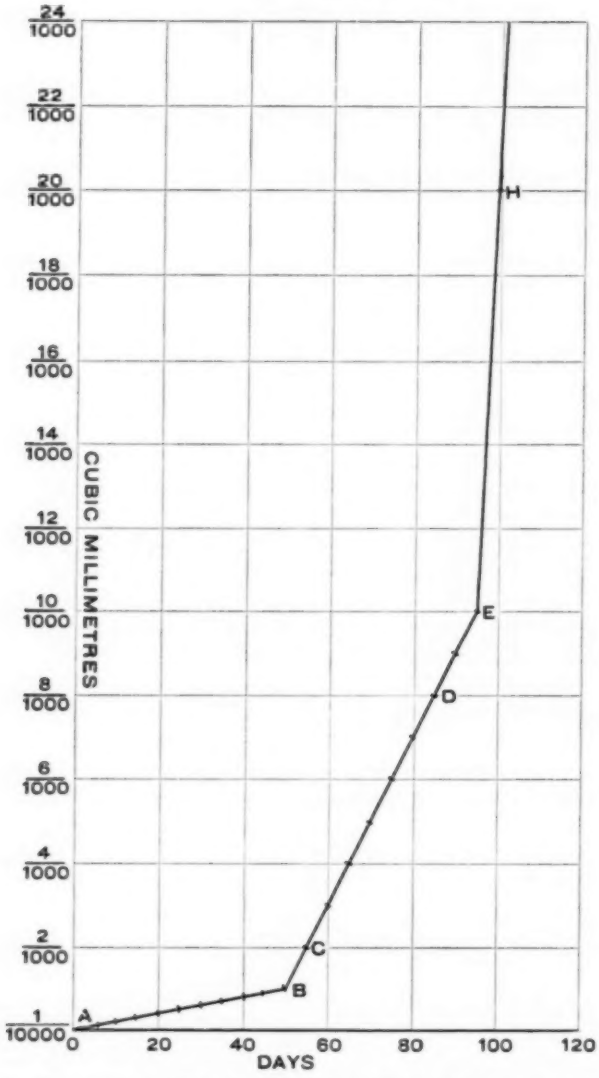


Fig. 1.—The usual method of administering Tuberculin; curve made up of different arithmetical series, A to B, B to E, etc. The sudden increase of dose from E to H is ten times the constant increase in section B to E, while B C is ten times the increase in A B. Interval between doses, five days.

cubic millimeter) being as great as the entire previous increase since the beginning of treatment (0 to 1/100 cubic millimeter), which has occupied ninety-five days and had been divided into nineteen doses.

Such a series as this certainly does not offer the uniformly progressive series of doses desired for administration to a patient so that the doses may increase *pari passu* with the resistance of the patient. On the contrary, we are inclined to believe that the sudden increase of doses with each new dilution is perhaps responsible for many of the unaccountable reactions, which it is so desirable to avoid in tuberculin therapy, "unaccountable" because these jumps are not manifest when shown in figures, but only when plotted as a curve.

To obtain a uniformly progressive series of doses such as we desire it is necessary to use a geometrical progression instead of an arithmetical progression. Such a curve is shown in Figure 2, where each dose is 25 per cent. larger than the preceding dose. It will be noted that there are no sudden jumps in this curve, the interval B′ C′ in Figure 2 (1/1,000 to 2/1,000) being covered by three doses instead of the one jump in the corresponding interval (B C) in Figure 1. At the end of the series the conditions are reversed and two doses are required to cover the distance D E, which in Figure 2 is covered in one dose (D′ E′). When the third series starts the large jump E H, in Figure 1, is covered in Figure 2 by three doses E′ H′.

It should be understood that in this geometrical curve the ratio (1.25) and the interval (four days) were both chosen to make the curve correspond as nearly as possible to Figure 1. Both curves cover a range of doses running from 1/10,000 to 2/100 cubic millimeters and a period of time of about one hundred days. In actual use both the ratio and the interval can be varied indefinitely, while still retaining the valuable characteristic of the smooth geometrical progression. Some patients may be able to stand an increase of 50 per cent., while for others it may be necessary to cut the increase down to 10 per cent.—in the one case the curve would rise more rapidly, in the other it would be flatter. The interval between doses can be either increased or decreased, as desired, or it can be made a variable. Figure 3 shows a curve similar to Figure 2, except that after every four doses the interval is increased by one day so that the small doses at the lower end of the curve are given at four-day intervals, the large doses at the upper end nine days apart, and the intermediate doses at increasing intervals.

Both of these curves are, of course, only suggestive of the type of curve it would seem desirable to follow: each patient must be given individual treatment. There is, however, a curve for each case, which, if

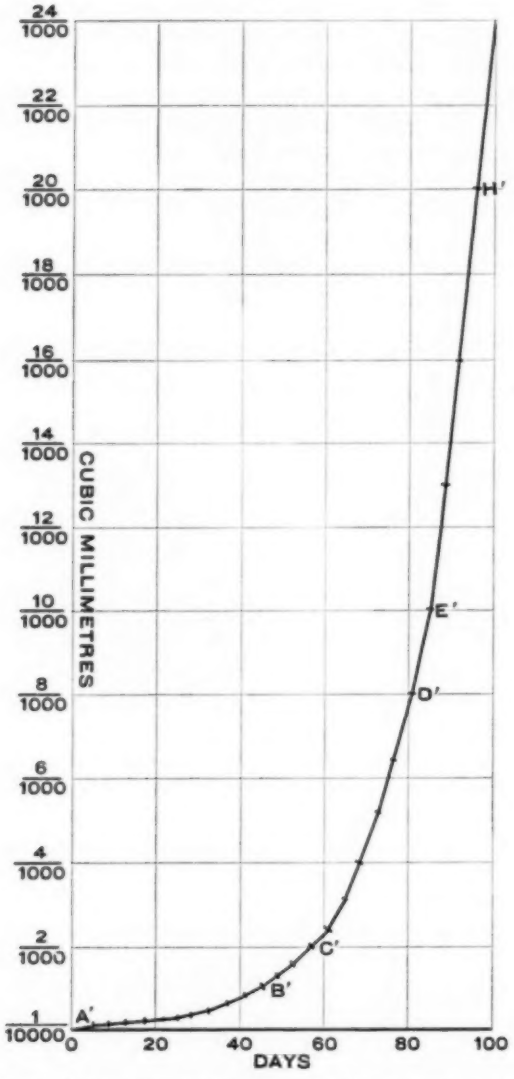


Fig. 2.—Curve showing progressive (geometrical) increase of dosage. Each dose is 25 per cent. larger than the preceding dose and the interval between doses four days.

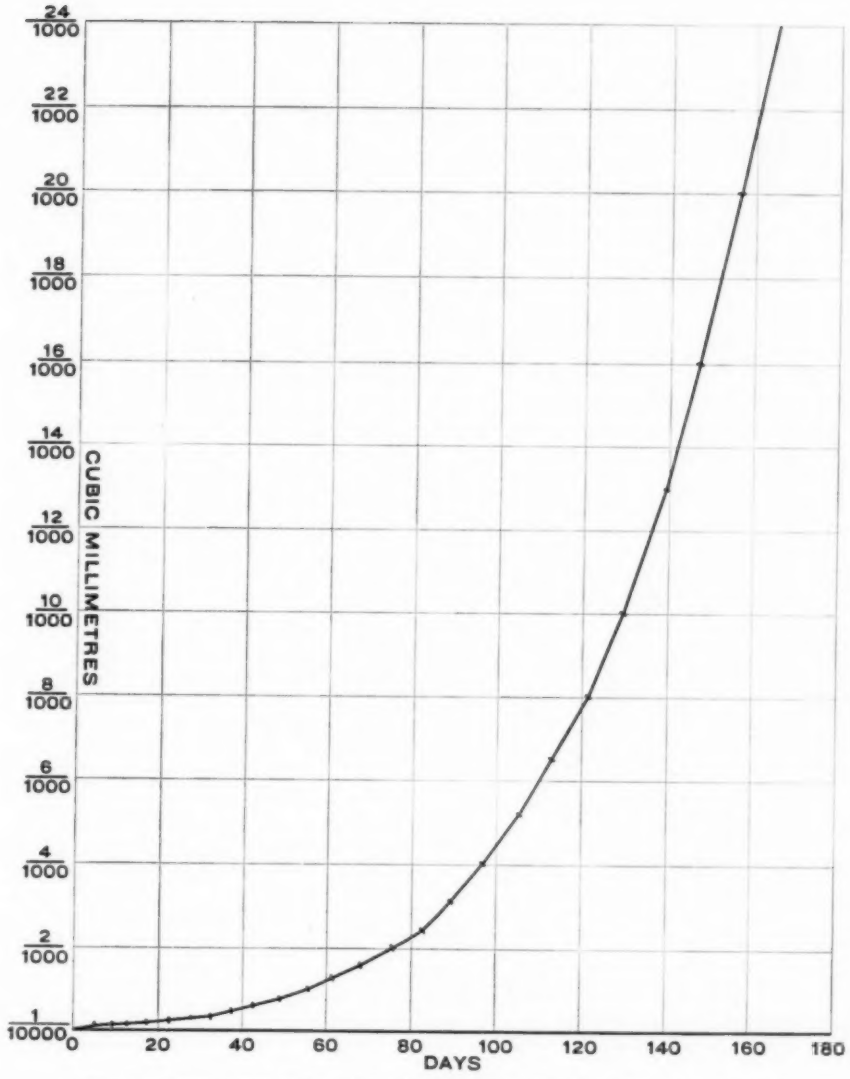


Fig. 3.—Curve same as in Figure 2, but after every four doses the interval between doses is increased by one day.

followed, will give the best results. The trouble is to find it. It would seem that the systematic plotting of the treatment of a case week by week as treatment progressed would, by the trend of the curve, be of value in suggesting further treatment; or, if a patient when brought up to a certain point showed signs of intolerance and an impending reaction so that it became necessary to interrupt treatment and then begin at a lower point, a curve of the case would show exactly the angle at which the critical point was approached before and would suggest the lower per cent. of increase which the patient might be able to keep up indefinitely.

The plotting of the curves of cases that have already passed through a course of tuberculin therapy might be instructive. The writer would be pleased to receive such curves or the case histories from which the curves could be plotted, and is willing to undertake the work involved in such a plotting in the hope that from a careful comparative study of a large number of cases some light may be thrown on the subject of tuberculin therapy.

The problem of obtaining suitable doses for such geometrical series is somewhat difficult, but by no means impossible. For a 25 per cent. increase the following series is approximately correct: 1, 1¼, 1½, 2, 2½, 3, 4, 5, 6, 8 and 10. Whether these numbers represent minims or tenths of a cubic centimeter, the first five are too small to be accurately measured. This can be overcome by having part of this solution diluted one to four, when the first five doses will be 4, 5, 6, 8 and 10 parts respectively, of the one-to-four dilution. In this and other ways suitable dilutions can be prepared for any series of doses. Physicians without laboratory facilities may find it convenient to have their pharmacists make the needed dilutions for them.

To sum up:

1. The serial dilutions of tuberculin now available when administered in doses of 1, 2, 3, 4, 5, 6, 7, 8 and 9 tenths of a cubic centimeter, or 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 minims do not give a uniformly progressive series of doses when passing from one dilution to the next.

2. In administering tuberculin each dose should be larger than the preceding by a certain per cent. (geometrical progression) rather than by a certain fixed quantity (arithmetical progression).

3. Plotting the treatment of each patient as a curve is advocated because of the light it may throw (a) on the treatment of the individual case and (b) on general tuberculin therapy.

TESTS CONCERNING TUBERCLE BACILLI IN THE CIRCULATING BLOOD

E. C. SCHROEDER AND W. E. COTTON
BETHESDA, MD.

On Dec. 10, 1908, Dr. Randle C. Rosenberger of the Jefferson Medical College, Philadelphia, Pa., read a paper before the Philadelphia Pathological Society on the occurrence of tubercle bacilli in the circulating blood. The paper was afterward published in *The American Journal of Medical Sciences* for February, 1909. In this paper he recorded that he had made microscopic examinations of the blood of 125 tuberculous individuals, some of whom were affected with only incipient tuberculosis, and that he had found tubercle bacilli in the blood of every one of these individuals. In some cases only a few bacilli were seen, but, to use his own words, "they were mostly in large numbers and clumps of 30 to 40 bacilli were not unusual, especially in cases of acute miliary tuberculosis." From his observations he formulated the conclusion, "It appears that tuberculosis in all its forms is a bacteriemia."

The occurrence of isolated tuberculous lesions in the bodies of otherwise tuberculous as well as otherwise healthy individuals, located in regions remote from the various channels that communicate with the exterior, gives the belief that tubercle bacilli occasionally float in the blood stream the character of a fact that is hardly open to question. The same is true when we consider cases of more or less generalized tuberculosis with many lesions in widely separated portions of the body, and cases of miliary tuberculosis with innumerable lesions of approximately, if not precisely, the same age and stage of development. But such occasional presence of tubercle bacilli in the circulating blood is a very different condition from their constant occurrence in it in sufficient numbers to justify the classification of tuberculosis as a bacteriemia. Hence, Rosenberger's conclusion was received with considerable surprise and decided incredulity.

Though the conclusion seems incredible, because it seems nearly impossible that a constant occurrence of tubercle bacilli in the blood of all tuberculous individuals could have been overlooked by the host of investigators who have studied tuberculosis with technic not greatly different from the one he used, we did not feel entitled to protest against it without offering some specific evidence to substantiate our protest.

Rosenberger stated that he found tubercle bacilli on microscopic examination in the blood of every one of the 125 cases of tuberculosis he studied, notwithstanding that some of the cases were incipient and failed to show tubercle bacilli in the sputum. It was, therefore, almost taken for granted that the microscopic examination of blood, according to his method, of animals affected with advanced and long standing tuberculosis and animals that were expelling tubercle bacilli from their bodies in large numbers, would reveal at least a few tubercle bacilli. A considerable number of such microscopic examinations were made, but not a tubercle bacillus was found in our blood preparations, and we have to record wholly negative results with the blood of tuberculous animals similar to the negative results obtained with the blood of tuberculous persons in two large New York hospitals.[1]

It is not uncommon for virulent tubercle bacilli to be present in animal substances in numbers too small to serve for their detection by optical methods. At the experiment station of the Bureau of Animal Industry, for example, we found the intra-abdominal injection of guinea-pigs with suspected milk to be a test for tubercle bacilli that has fully 50 times the delicacy of a microscopic examination. Furthermore, tinctorial and optical methods of distinguishing between tubercle bacilli and other acid-fast bacteria are not wholly satisfactory; hence we decided to inject a sufficient number of guinea-pigs with blood from a sufficient number of certainly tuberculous cattle to show conclusively either that tubercle bacilli are commonly present in such blood or that they are not commonly present in such blood.

Incidentally we wish to say that Dr. Rosenberger's work is very weak in the extent to which he confirmed, by animal experiments, his surprising microscopic observations, which would be of the greatest value if true alone for the early and certain diagnosis of tuberculosis. In all he inoculated only two guinea-pigs of which he gives records—one with blood from a tuberculous person who was expelling tubercle bacilli per rectum and one with blood from a patient with acute miliary tuberculosis.

The development of tuberculosis in the latter guinea-pig can not be regarded as a remarkable phenomenon; there is nothing about the fact that a guinea-pig contracted tuberculosis after an injection of blood obtained from a case of acute miliary tuberculosis that necessitates a modification of our currently accepted views on the presence of tubercle bacilli in the circulating blood. That is to say, we need not look on tuberculosis as a bacteriemia because tubercle bacilli were demonstrated

1. Editorial in Med. Rec., New York, 1909, lxxv, 568.

in blood, in which we have long taken their occurrence as a matter of course.

This leaves one guinea-pig that may have some evidential value, but we must not lose sight of the fact that it was injected with blood obtained from a person who was expelling tubercle bacilli from his body, and, hence, to some extent infecting his environment. We must also bear in mind that guinea-pigs are highly susceptible to tubercle bacilli injected into their bodies and that it is often impossible for an investigator who handles much tuberculous material, who is in frequent contact with tuberculous persons and whose environment may be characterized as containing tubercle bacilli, to eliminate all danger of extraneous tuberculous infection sufficiently to make a test satisfactory when he seeks to verify the tuberculous character of some material from a tuberculous individual by the injection of one, and only one, guinea-pig.

Our own tests, which follow, were made entirely with the blood of tuberculous cattle. In every case the blood was drawn from the jugular vein of the tuberculous animal and injected in its fresh, naturally warm state into the peritoneal cavity of a guinea-pig. The tuberculous cattle, as their records show, may be divided into four distinct lots according to the knowledge we have of their tuberculous condition.

Lot 1.—Four cattle, the precise tuberculous condition of which is known because they were killed and examined postmortem shortly after the blood was drawn from them for guinea-pig injections.

Lot 2.—Six cattle, known to be tuberculous because they had reacted with tuberculin, because tubercle bacilli were found in their feces on microscopic examination and because their feces were proven to be infectious by animal experiments.

Lot 3.—Nineteen cattle, known to be tuberculous because they had reacted with tuberculin and because tubercle bacilli were found in their feces on microscopic examination.

Lot 4.—Thirteen cattle, known to be tuberculous because they had reacted with tuberculin.

We made no attempt to treat the blood used for the injections in any way, because we assumed that the best results would be obtained with it by transferring it as rapidly as possible from the tuberculous cattle to the peritoneal cavities of the guinea-pigs. It was learned from the injections that guinea-pigs tolerate a relatively large quantity of bovine blood in their peritoneal cavity. The guinea-pigs that died shortly after and as the result of the blood injections, about 15 per cent. of all injected, with few exceptions showed extreme impaction and some

inflammation of the large bowel, associated in several instances with invagination of the colon.

The possibility exists that the intraperitoneal injection of from 3 to 5 c.c. of fresh, warm blood from tuberculous cattle induces an immunity in guinea-pigs to the tubercle bacilli the blood may contain. Though this view is purely hypothetical and we know nothing to sustain it, we have undertaken an investigation to prove or disprove it, and will append the results to this article if they are ready before it goes to the printer.

The total number of cattle from which blood injections were made is 42, and these, as their records show, represent a considerable variety relative to the severity and extent of the tuberculous disease with which they are affected, from animals that would not have been suspected to be diseased without a tuberculin test to a cow so badly affected that a calf of which she became the mother, a little less than a year before her blood was used for guinea-pig injections, was born affected with tuberculosis contracted from antepartum exposure to her tuberculous body.

The total number of guinea-pigs injected was 104. Of these 16 died within a few days after the injection and no doubt as a result of it, 3 died of intercurrent affections, but not until a sufficient period of time had passed for lesions of tuberculosis to become clearly manifest, and 85 guinea-pigs lived until they were killed after a lapse of from seven and one-half to eleven weeks, or an average for all of seventy days after they were injected. The 3 guinea-pigs that died of intercurrent affections showed no lesions of tuberculosis on postmortem examination, and 84 of the 85 guinea-pigs that lived until they were killed showed no lesions of any kind on autopsy. One guinea-pig of the 85 showed lesions very slightly resembling tuberculosis, but these were proved by microscopic examinations and guinea-pig inoculation tests to be free from tubercle bacilli.

A detailed record of the cattle and guinea-pigs used in our tests follows:

RECORD OF TUBERCULOUS CATTLE AND GUINEA-PIGS

CATTLE, LOT 1

Bull 393, general condition very good, affected with tuberculosis a year or more, was killed and examined postmortem on April 8, 1909. The autopsy revealed only one small tuberculous lesion located in one of the superficial inguinal glands.

On Feb. 5, 1909, two guinea-pigs, Nos. 2891 and 2892, received each an intra-abdominal injection of 2 c.c. of blood from the bull. One guinea-pig, No. 2891, died on Feb. 14, 1909, affected with invagination of the bowel. The other guinea-pig remained healthy until April 13, 1909 (sixty-seven days after injection), when it was killed and found on postmortem examination to be free from lesions of disease.

Cow 533, general condition poor, affected with tuberculosis two years or more, was killed and examined postmortem on April 24, 1909. The autopsy revealed the following conditions; the principal lobe of the right lung contained a cavity about three inches in diameter, partly filled with pasty, necrotic, tuberculous material. This cavity was in direct communication with a large bronchial tube, which contained a considerable amount of material discharged from the cavity. Sprinkled throughout the lungs generally, a number of smaller tuberculous foci, in a completely broken-down condition, were found. The mediastinal and mesenteric lymph glands and the liver were sprinkled with tuberculous foci, some of which were as much as one-half inch in diameter.

Prior to the cow's death her feces were examined microscopically on nine different days and on six of these days were found to contain tubercle bacilli.

On Feb. 3, 1909, two guinea-pigs, Nos. 2859 and 2860, received each an intra-abdominal injection of 3 c.c. of blood of the cow. The guinea-pigs remained healthy until April 13, 1909 (sixty-nine days after injection), when they were killed and found on postmortem examination to be free from lesions of disease.

Cow 549, general condition poor, affected with tuberculosis several years, on March 27, 1908, gave birth to a calf affected with congenital tuberculosis. The cow was killed on April 8, 1909, and on autopsy was found to be affected with advanced, generalized tuberculosis. The lungs contained lesions varying from quite recent tuberculous disease to large tuberculous cavities that had discharged most of their contents through the bronchial tubes.

No tests were made relative to the infectious character of the feces before death.

On Feb. 3, 1909, two guinea-pigs, Nos. 2863 and 2864, received each an intra-abdominal injection of 3 c.c. of blood from the cow. The guinea-pigs were killed on April 13, 1909 (sixty-nine days after injection), and on postmortem examination were found to be free from lesions of disease.

Cow 552, general condition poor, affected with tuberculosis several years, was killed on April 1, 1909. The autopsy revealed a fairly generalized tuberculosis with lesions of greater or lesser magnitude in the lungs and in the pharyngeal, bronchial and mesenteric lymph glands.

Prior to the cow's death her feces were examined microscopically on ten different days, and on six of these days were found to contain tubercle bacilli.

Hogs that were fed feces from the cow contracted tuberculosis, and guinea-pigs inoculated subcutaneously with small masses of her feces likewise contracted tuberculosis.

Guinea-pigs were injected intra-abdominally with blood from this cow as follows:

Jan. 25, 1909, Guinea-pig 2785 received 5 c.c. of blood.
Jan. 25, 1909, Guinea-pig 2786 received 5 c.c. of blood.
Jan. 25, 1909, Guinea-pig 2783 received 2.5 c.c. of blood.
Jan. 25, 1909, Guinea-pig 2784 received 2.5 c.c. of blood.
Jan. 25, 1909, Guinea-pig 2781 received 1 c.c. of blood.
Jan. 25, 1909, Guinea-pig 2782 received 1 c.c. of blood.
Feb. 3, 1909, Guinea-pig 2861 received 3 c.c. of blood.
Feb. 3, 1909, Guinea-pig 2862 received 3 c.c. of blood.
Feb. 5, 1909, Guinea-pig 2889 received 2.5 c.c. of blood.
Feb. 5, 1909, Guinea-pig 2890 received 2.5 c.c. of blood.

Guinea-pigs 2786 and 2890 died prematurely as a result of the blood injections, and the remaining eight guinea-pigs were killed on the following dates and on autopsy were found to be free from lesions of disease.

Guinea-pigs 2781 and 2782, killed March 27, 1909 (sixty-one days after injection).

Guinea-pigs 2783 and 2784, killed April 13, 1909 (seventy-eight days after injection).

Guinea-pig 2785, killed April 12, 1909 (seventy-eight days after injection).

Guinea-pig 2889, killed April 13, 1909 (sixty-seven days after injection).

Guinea-pigs 2861 and 2862, killed April 13, 1909 (sixty-nine days after injection).

CATTLE, LOT 2

Cow 511, general condition poor, has been affected with tuberculosis eighteen months or more. Microscopic examinations of the feces on seven different days revealed tubercle bacilli on three days. A hog fed with feces from the cow contracted tuberculosis.

On Feb. 1, 1909, two guinea-pigs, Nos. 2829 and 2830, received each an intra-abdominal injection of 3 c.c. of blood from the cow. The guinea-pigs remained healthy until April 13, 1909 (seventy-one days after injection), when they were killed and found on autopsy to be free from lesions of disease.

Cow 537, general condition fairly good, has been affected with tuberculosis more than two years. Microscopic examinations of the feces on fifteen days revealed tubercle bacilli on eleven days. Guinea-pigs inoculated with small masses of feces contracted tuberculosis.

Guinea-pigs were injected, intra-abdominally, with blood from the cow as follows:

Feb. 4, 1909, Guinea-pig 2871 received 3 c.c. of blood.
Feb. 4, 1909, Guinea-pig 2872 received 3 c.c. of blood.
Feb. 19, 1909, Guinea-pig 3062 received 3 c.c. of blood.
Feb. 19, 1909, Guinea-pig 3063 received 3 c.c. of blood.

Guinea-pig 2872 died prematurely as a result of the injection.

Guinea-pig 2871 was killed on April 13, 1909 (sixty-eight days after injection), and on autopsy was found to be free from lesions of disease. Guinea-pigs 3062 and 3063 were killed on April 13, 1909 (fifty-three days after injection), and on autopsy were found to be free from lesions of disease.

Cow 538, general condition very poor, has been affected with tuberculosis two years or longer. Microscopic examinations of feces on eleven different days revealed tubercle bacilli on nine days. Guinea-pigs inoculated with small masses of feces, and hogs fed feces of this cow, contracted tuberculosis.

On Feb. 3, 1909, two guinea-pigs, Nos. 2851 and 2852, received each an intra-abdominal injection of 3 c.c. of blood from the cow. On April 13, 1909 (sixty-nine days after the injection), the guinea-pigs were killed and on autopsy found to be free from lesions of disease.

Cow 555, general condition fairly good, has been affected with tuberculosis more than two years. Microscopic examinations of feces on five different days revealed tubercle bacilli on two days. A hog fed feces from the cow contracted tuberculosis.

On Jan. 30, 1909, two guinea-pigs, Nos. 2811 and 2812, received each an intra-abdominal injection of 3 c.c. of blood from the cow. Guinea-pig 2811 died prematurely as a result of the injection. Guinea-pig 2812 was killed on April 12, 1909 (seventy-two days after injection) and on postmortem examination was found to be free from lesions of disease.

Cow 567, general condition good, has been affected with tuberculosis at least two and a half years. Microscopic examinations of feces on ten different days revealed tubercle bacilli on five days. A hog fed with feces from the cow contracted tuberculosis.

On Feb. 4, 1909, two guinea-pigs, Nos. 2869 and 2870, received each an intra-abdominal injection of 3 c.c. of blood from the cow. The guinea-pigs were killed

on April 12, 1909 (sixty-seven days after injection), and on autopsy were found to be free from lesions of disease.

Cow 646, general condition fair, has been affected with tuberculosis for some time, but it is not known just how long. Microscopic examinations of feces on two different days revealed tubercle bacilli on one day. Guinea-pigs inoculated with her feces contracted tuberculosis.

On Feb. 2, 1909, two guinea-pigs, Nos. 2847 and 2848, received each an intra-abdominal injection of 3 c.c. of blood from the cow. The guinea-pigs were killed on April 13, 1909 (seventy days after injection), and on autopsy were found to be free from lesions of disease.

CATTLE, LOT 3

Cow 503, general condition good, has been affected with tuberculosis at least two and a half years. Microscopic examinations of feces on two days revealed tubercle bacilli on one day.

On Jan. 30, 1909, two guinea-pigs, Nos. 2805 and 2806, received each an intra-abdominal injection of 3 c.c. of blood from the cow. The guinea-pigs were killed on April 30, 1909 (seventy-three days after injection), and on autopsy were found to be free from lesions of disease.

Cow 510, general condition fairly good, has been affected with tuberculosis about three years. Microscopic examinations of feces on three days revealed tubercle bacilli on two days.

Guinea-pigs injected intra-abdominally with blood from the cow as follows:

Jan. 29, 1909, Guinea-pig 2791 received 5 c.c.
Jan. 29, 1909, Guinea-pig 2792 received 5 c.c.
Feb. 4, 1909, Guinea-pig 2881 received 3 c.c.
Feb. 4, 1909, Guinea-pig 2882 received 3 c.c.

Guinea-pigs 2791 and 2792 died prematurely as a result of the injections. Guinea-pigs 2881 and 2882 were killed on April 13, 1909 (sixty-eight days after injection), and on autopsy were found to be free from lesions of disease.

Cow 512, general condition good, has been affected with tuberculosis eighteen months or longer. Microscopic examinations of feces on six different days revealed tubercle bacilli on four days.

On Feb. 11, 1909, two guinea-pigs, Nos. 2823 and 2824, received each an intra-abdominal injection of 3 c.c. of blood from the cow. The guinea-pigs were killed on April 12, 1909 (seventy days after injection), and on autopsy were found to be free from lesions of disease.

Cow 513, general condition fairly good, but with greatly enlarged throat glands, has been affected with tuberculosis eighteen months or longer. Microscopic examinations of feces on four different days revealed tubercle bacilli on two days.

On Feb. 2, 1909, two guinea-pigs, Nos. 2835 and 2836, received each an intra-abdominal injection of 3 c.c. of blood from the cow. Guinea-pig 2835 died prematurely as a result of the injection. Guinea-pig 2836 was killed on April 12, 1909 (sixty-nine days after injection), and on autopsy was found to be free from lesions of disease.

Cow 514, general condition poor, has been affected with tuberculosis about three years. Microscopic examinations of feces on three different days revealed tubercle bacilli on one day.

On Jan. 30, 1909, two guinea-pigs, Nos. 2815 and 2816, received each an intra-abdominal injection of 3 c.c. of blood from the cow. Guinea-pig 2816 died of an intercurrent affection on March 3, 1909 (thirty-two days after injection), and on autopsy was found to be free from lesions of tuberculosis. Guinea-pig 2815 was killed on April 12, 1909 (seventy-two days after injection), and on autopsy was found to be free from lesions of disease.

Cow 515, general condition fairly good, has been affected with tuberculosis eighteen months or longer. Microscopic examinations of feces on seven different days revealed tubercle bacilli on four days.

On Feb. 1, 1909, two guinea-pigs, Nos. 2821 and 2822, received each an intra-abdominal injection of 3 c.c. of blood from the cow. The guinea-pigs were killed on April 12, 1909 (seventy days after injection), and on autopsy were found to be free from lesions of disease.

Cow 516, general condition fairly good, has been affected with tuberculosis eighteen months or longer. Microscopic examinations of feces on seven different days revealed tubercle bacilli on four days.

On Feb. 1, 1909, two guinea-pigs, Nos. 2831 and 2832, received each an intra-abdominal injection of 3 c.c. of blood from the cow. The guinea-pigs were killed on April 13, 1909 (seventy-one days after injection), and on autopsy were found to be free from lesions of disease.

Cow 536, general condition poor, has been affected with tuberculosis two years or longer. Microscopic examinations of feces on eleven different days revealed tubercle bacilli on eight days.

On Feb. 3, 1909, two guinea-pigs, Nos. 2865 and 2866, received each an intra-abdominal injection of 3 c.c. of blood from the cow. The guinea-pigs were killed on April 13, 1909 (sixty-nine days after injection), and on autopsy were found to be free from lesions of disease.

Cow 561, general condition fairly good, has been affected with tuberculosis two years or longer. Microscopic examinations of feces on nine different days revealed tubercle bacilli on three days.

On Feb. 1, 1909, two guinea-pigs, Nos. 2833 and 2834, received each an injection of 3 c.c. of blood from the cow. The guinea-pigs were killed on April 12, 1909 (seventy days after the injection), and on autopsy were found to be free from lesions of disease.

Cow 553, general condition fairly good, has been affected with tuberculosis two years or longer. Microscopic examinations of feces on three different days revealed tubercle bacilli on every day.

On Feb. 1, 1909, two guinea-pigs, Nos. 2827 and 2828, received each an intra-abdominal injection of 3 c.c. of blood from the cow. The guinea-pigs were killed on April 13, 1909 (seventy-one days after the injection), and on autopsy were found to be free from lesions of disease.

Cow 620, general condition good, has been affected with tuberculosis a year or longer. Microscopic examinations of feces on four different days revealed tubercle bacilli on one day.

On Feb. 3, 1909, two guinea-pigs, Nos. 2855 and 2856, received each an intra-abdominal injection of 3 c.c. of blood from the cow. The guinea-pigs were killed on April 13, 1909 (sixty-nine days after the injection), and on autopsy were found to be free from lesions of disease.

Cow 629, general condition fair, has been affected with tuberculosis at least one year. Microscopic examinations of feces on five different days revealed tubercle bacilli on two days.

On Feb. 3, 1909, two guinea-pigs, Nos. 2857 and 2858, received each an intra-abdominal injection of 3 c.c. of blood from the cow. The guinea-pigs were killed on April 13 (sixty-nine days after the injection), and on autopsy were found to be free from lesions of disease.

Cow 631, general condition fair, has been affected with tuberculosis at least one year. Microscopic examinations of feces on four different days revealed tubercle bacilli on one day.

On Feb. 4, 1909, two guinea-pigs, Nos. 2877 and 2878, received each an intra-abdominal injection of 3 c.c. of blood from the cow. The guinea-pigs were killed

on April 13, 1909 (sixty-eight days after the injection), and on autopsy were found to be free from lesions of disease.

Bull 635, general condition good, has been affected with tuberculosis over two years. Microscopic examinations of feces on three different days revealed tubercle bacilli on one day.

On Jan. 20, 1909, two guinea-pigs, Nos. 2817 and 2818, received each an intra-abdominal injection of 3 c.c. of blood from the bull. Guinea-pig 2818 died prematurely as a result of the injection. Guinea-pig 2817 was killed on April 12, 1909 (seventy-two days after the injection), and on autopsy was found to be free from lesions of disease.

Cow 636, general condition fairly good, has been affected with tuberculosis at least one year. Microscopic examinations of feces on five different days revealed tubercle bacilli on two days.

On Jan. 30, 1909, two guinea-pigs, Nos. 2803 and 2804, received each an intra-abdominal injection of 3 c.c. of blood from the cow. The guinea-pigs were killed on April 12, 1909 (seventy-two days after the injection), and on autopsy were found to be free from lesions of disease.

Cow 638, general condition fairly good, has been affected with tuberculosis over two years. Microscopic examinations of feces on four different days revealed tubercle bacilli on all four days.

Guinea-pigs were given intra-abdominal injections of the blood of this cow as follows:

Jan. 29, 1909, Guinea-pig 2795 received 5 c.c.
Jan. 29, 1909, Guinea-pig 2796 received 5 c.c.
Feb. 4, 1909, Guinea-pig 2879 received 3 c.c.
Feb. 4, 1909, Guinea-pig 2880 received 3 c.c.

Guinea-pig 2795 died prematurely as a result of the injection. Guinea-pig 2796 was killed on April 12, 1909 (seventy-three days after the injection), and on autopsy was found to be free from lesions of disease. Guinea-pigs 2879 and 2880 were killed on April 12, 1909 (sixty-seven days after injection), and on autopsy were found to be free from lesions of disease.

Cow 639, general condition good, has been affected with tuberculosis at least one year. Microscopic examinations of feces on four different days revealed tubercle bacilli on one day.

Guinea-pigs were given intra-abdominal injections of the blood of this cow as follows:

Jan. 29, 1909, Guinea-pig 2801 received 5 c.c.
Jan. 29, 1909, Guinea-pig 2802 received 5 c.c.
Feb. 5, 1909, Guinea-pig 2887 received 3 c.c.
Feb. 5, 1909, Guinea-pig 2888 received 3 c.c.

Guinea-pig 2801 died prematurely as a result of the injection. Guinea-pig 2802 was killed April 12, 1909 (seventy-three days after the injection), and on autopsy several necrotic foci were found in the liver and spleen. The lesions were not at all like the conditions caused by the tubercle bacillus and microscopic examinations failed to reveal tubercle bacilli. Some of the abnormal tissue was used to make subinoculations into guinea-pigs; the subinoculated guinea-pigs failed to show tuberculosis.

Guinea-pigs 2887 and 2888 were killed on April 13, 1909 (sixty-seven days after the injection), and on autopsy were found to be free from lesions of disease.

Cow 640, general condition good, has been affected with tuberculosis over two years. Microscopic examinations of feces on three different days revealed tubercle bacilli on all three days.

On Jan. 29, 1909, two guinea-pigs, Nos. 2799 and 2800, received each an intra-abdominal injection of 5 c.c. of blood from the cow. The guinea-pigs were killed

on April 12, 1909 (seventy-three days after the injection), and on autopsy were found to be free from lesions of disease.

Cow 642, general condition good, has been affected with tuberculosis at least one year. Microscopic examinations of feces on three different days revealed tubercle bacilli on two days.

Guinea-pigs were injected intra-abdominally with blood from this cow as follows:

Jan. 29, 1909, Guinea-pig 2793 received 5 c.c.
Jan. 29, 1909, Guinea-pig 2794 received 5 c.c.
Feb. 5, 1909, Guinea-pig 2885 received 3 c.c.
Feb. 5, 1909, Guinea-pig 2886 received 3 c.c.

Guinea-pig 2794 died prematurely as the result of the injection. Guinea-pig 2886 died on March 5, 1909 (twenty-eight days after the injection), of an intercurrent affection; the autopsy revealed no lesions resembling tuberculosis. Guinea-pig 2793 was killed on April 13, 1909 (seventy-three days after injection), and on autopsy was found to be free from lesions of disease. Guinea-pig 2885 was killed on April 13, 1909 (sixty-seven days after injection), and on autopsy was found to be free from lesions of disease.

CATTLE, LOT 4

Cow 479, general condition fair, but with greatly enlarged throat glands, has been affected with tuberculosis about three years.

On Feb. 4, 1909, two guinea-pigs, Nos. 2873 and 2874, received each an intra-abdominal injection of 3 c.c. of her blood. The guinea-pigs were killed on April 13, 1909 (sixty-eight days after injection), and on autopsy were found to be free from lesions of disease.

Bull 508, general condition good, has been affected with tuberculosis about two and a half years.

On Feb. 4, 1909, two guinea-pigs, Nos. 2867 and 2868, received each an intra-abdominal injection of 3 c.c. of his blood. The guinea-pigs were killed on April 12, 1909 (sixty-seven days after injection), and on autopsy were found to be free from lesions of disease.

Cow 517, general condition good, has been affected with tuberculosis about two and a half years.

On Feb. 1, 1909, two guinea-pigs, Nos. 2825 and 2826, received each an intra-abdominal injection of 3 c.c. of her blood. Guinea-pig 2825 died of an intercurrent affection on April 5, 1909 (sixty-three days after injection), and on autopsy was found to be free from lesions of tuberculosis. Guinea-pig 2826 was killed April 13, 1909 (seventy-one days after injection), and on autopsy was found to be free from lesions of disease.

Cow 569, general condition fair, has been affected with tuberculosis about two years.

On Feb. 1, 1909, two guinea-pigs, Nos. 2819 and 2820, received each an intra-abdominal injection of 3 c.c. of her blood. The guinea-pigs were killed April 12, 1909 (seventy days after injection), and on autopsy were found to be free from lesions of disease.

Cow 630, general condition fair, has been affected with tuberculosis about one year.

On Feb. 3, 1909, two guinea-pigs, Nos. 2853 and 2854, received each an intra-abdominal injection of 3 c.c. of her blood. The guinea-pigs were killed April 13, 1909 (sixty-nine days after the injection), and on autopsy were found to be free from lesions of disease.

Cow 632, general condition good, has been affected with tuberculosis at least one year.

On Jan. 30, 1909, two guinea-pigs, Nos. 2807 and 2808, received each an intra-abdominal injection of 3 c.c. of her blood. Guinea-pig 2808 died prematurely as a result of the injection. Guinea-pig 2807 was killed on April 13, 1909 (seventy-two days after the injection), and on autopsy was found to be free from lesions of disease.

Cow 634, general condition fair, has been affected with tuberculosis at least one year.

On Jan. 29, 1909, two guinea-pigs, Nos. 2787 and 2788, received each an intra-abdominal injection of 5 c.c. of her blood. The guinea-pigs were killed on April 12, 1909 (seventy-three days after the injection), and on autopsy were found to be free from lesions of disease.

Cow 641, general condition fair, has been affected with tuberculosis over two years.

On Jan. 29, 1909, two guinea-pigs, Nos. 2797 and 2798, received each an intra-abdominal injection of 5 c.c. of the blood of the cow, and on Feb. 4, 1909, two guinea-pigs, Nos. 2875 and 2876, received each a similar injection of 3 c.c. of blood. Guinea-pig 2798 died prematurely as a result of the injection. Guinea-pig 2797 was killed on April 12, 1909 (seventy-five days after the injection), and guinea-pigs 2875 and 2876 were killed on April 12, 1909 (sixty-seven days after the injection). The three guinea-pigs were found to be free from lesions of disease.

Cow 644, general condition fair, has been affected with tuberculosis four months or more.

On Feb. 2, 1909, two guinea-pigs, Nos. 2849 and 2850, received each an intra-abdominal injection of 3 c.c. of blood of the cow. The guinea-pigs were killed on April 13, 1909 (seventy days after the injection), and on autopsy were found to be free from lesions of disease.

Cow 645, general condition good, has been affected with tuberculosis three months or more.

On Feb. 2, 1909, two guinea-pigs, Nos. 2845 and 2846, received each an intra-abdominal injection of 3 c.c. of her blood. Guinea-pig 2845 died prematurely as a result of the injection. Guinea-pig 2846 was killed on April 13, 1909 (seventy days after the injection), and on autopsy was found to be free from lesions of disease.

Cow 648, general condition good, has been affected with tuberculosis an unknown period of time. She was brought to the experiment station only shortly before her blood was used for guinea-pig injections and reacted with tuberculin.

On Feb. 2, 1909, two guinea-pigs, Nos. 2837 and 2838, received each an intra-abdominal injection of 3 c.c. of her blood. The guinea-pigs were killed on April 12, 1909 (sixty-nine days after the injection), and on autopsy were found to be free from lesions of disease.

Cow 657, general condition fair, has been affected with tuberculosis an unknown period of time. She was brought to the experiment station only shortly before her blood was used for guinea-pig injections, and reacted with tuberculin.

On Feb. 2, 1909, two guinea-pigs, Nos. 2841 and 2842, received each an intra-abdominal injection of 3 c.c. of her blood. The guinea-pigs were killed on April 12, 1909 (sixty-nine days after the injection), and on autopsy were found to be free from lesions of disease.

The 42 cattle included in the records are all those that were available for this investigation among the tuberculous cattle kept for various purposes at the Bureau of Animal Industry Experiment Station. The general condition of the cattle is briefly defined as good, fairly good, fair or poor, and, as these terms are used somewhat arbitrarily, it is desirable to specify more precisely the ideas they are intended to convey.

The word "good" is used in connection with cattle that are really in excellent, visible, physical condition and in which no one would suspect disease; the words "fairly good" are used to mean that condition commonly found among dairy cows of the better class; "fair" is used to designate a condition which the average dairyman regards as satisfactory, and the word "poor" is used to qualify all cattle that are thin or that show visible symptoms of disease.

Among the 42 cattle 27, or 64.25 per cent., were shown by microscopic examinations to be discharging tubercle bacilli from their bowels, in most instances intermittently, and the infectious character of the feces of 7 of the 42 cattle, or 16⅔ per cent., was proved by animal experiments; that is, feeding and inoculation tests.

The two facts, that 27 of the cattle were shown by microscopic tests to be expelling tubercle bacilli per rectum and that only 7 were proved by animal experiments to be passing infected feces, must not be taken as being in any sense contradictory, as the feces of only a sufficient number of tuberculous cattle were tested by animal feeding and inoculation experiments to prove conclusively that the acid-fast bacilli found on microscopic examinations in the feces of tuberculous cattle are certainly live, virulent tubercle bacilli.

Relative to the expulsion of tubercle bacilli from the bowels of tuberculous cattle, we wish to say that all the evidence we have indicates that the bacilli have their origin in the lungs and throat, from which regions they are coughed up, swallowed, and passed through and out of the intestinal canal without appreciable loss of pathogenic virulence. That a large proportion of the tubercle bacilli swallowed by cattle really pass through their bodies and out per rectum, without a determinable loss of virulence, was experimentally shown in some of our earlier work.[2] We have absolutely no reason to believe that tubercle bacilli enter the intestinal canal from the lymph radicles or blood capillaries, or by any complex and mysterious system of transportation from lesions of all descriptions and kinds in any or every portion of the body. It is our conviction that, unless an open tuberculosis is in more or less direct communication with the intestinal canal or there is a tuberculous disease of the intestine itself, which latter is rare among cattle, no tubercle bacilli will be expelled with the feces.

If tuberculosis in all its forms was a bacteriemia, the expulsion of tubercle bacilli from the bowels of all tuberculous individuals, as well

2.. Bull. 88 and 99, Bureau of Animal Industry.

as with their urine, saliva, milk and other bodily secretions, would follow as a natural consequence. Those who have carefully studied the secretions from the uninvolved organs of tuberculous subjects know how rarely tubercle bacilli are detected in them, even with the application of the most delicate tests.

When we consider cattle like Nos. 533, 549 and 552, three of the four animals of which autopsy records are given, and note that they were so badly diseased that they would have been condemned on superficial examination as wholly unfit for use as food under the existing meat inspection regulations, the absence of tubercle bacilli from their blood may be regarded as a sufficient reason for assuming that the possible occurrence of tubercle bacilli in the blood of tuberculous animals will almost invariably be associated with pathologic conditions of a very marked character, or that the tubercle bacilli will be present in extremely small numbers and will speedily be filtered out of the blood stream. Cow 533 had been affected with tuberculosis two years or longer, was in poor condition as a result of the disease, and on autopsy was found to have an extensive, open tuberculosis of the lung, and lesions of tuberculosis in the liver, and in both the thoracic and abdominal lymph glands. Cow 549 was, if anything, even more severely and extensively affected, and less than a year before her blood was injected into guinea-pigs had given birth to a congenitally tuberculous calf. Cow 552 was also affected with generalized, advanced, open tuberculosis, and prior to the use of her blood for guinea-pig injections was found to be passing large numbers of tubercle bacilli from her bowels, which were proved by feeding tests to be virulent for hogs, and by inoculation tests to be virulent for guinea-pigs. With the blood obtained from these 3 cows 14 guinea-pigs were injected, 12 of which lived two months or more afterward, until they were intentionally killed, when they were found on postmortem examination to be wholly free from lesions of disease of any kind.

The possibility exists that tubercle bacilli introduced into the stomach and intestine by swallowing may be taken up by the lymph radicles, passed along the lymph channels and emptied through the great lymph ducts into the venous circulation. The investigations of Nicolas and Descos, Ravenel, Calmette and Guerin, Schlossman and Engle, and others speak for this, but such tubercle bacilli will not be very numerous and will no doubt be filtered out of the blood as soon as it reaches the lung through the heart and pulmonary arteries, to which it passes directly after it has received the lymph stream.

CONCLUSIONS

We failed utterly to find tubercle bacilli in the blood of tuberculous cattle which we examined microscopically in accordance with the method described and used by Dr. Rosenberger.

The negative results of our microscopic examinations are confirmed by the negative results obtained with 88 guinea-pigs, each of which received an intra-abdominal injection of blood from a tuberculous cow or bull.

As the number of cattle from which blood was injected into the 88 guinea-pigs is 42, and as these cattle represented practically all stages of tuberculosis, from mildly affected, recent cases to old and completely generalized cases, we feel that our work shows beyond the remotest doubt that tuberculosis is not to be classified, in any sense of the word, as a bacteriemia.

SUPPLEMENT

In the foregoing article we made the statement: "The possibility exists that the intraperitoneal injection of from 3 to 5 c.c. of fresh, warm blood from tuberculous cattle induces an immunity in guinea-pigs to the tubercle bacilli the blood may contain. Though this view is purely hypothetical and we know of nothing to sustain it, we have undertaken an investigation to prove or disprove it, and will append the results to this article if they are ready before it goes to the printer." The results of the additional investigation are now ready and are given in this supplement.

On April 24, 1909, blood and tuberculous material were obtained from Cow 533 (see record 8) for a number of guinea-pig injections. The primary object of the injections was to prove that the blood of a tuberculous cow, when introduced into the peritoneal cavity of a guinea-pig, has no retarding influence on the development of tuberculosis from tubercle bacilli that may be present in such blood.

Cow 533 was first bled from the jugular vein and then at once killed. As soon as she was dead a tuberculous mediastinal gland was removed from her body and 500 mg. of it emulsified with 2 c.c. of sterile, normal salt solution. Cover-glasses of this emulsion, stained with carbolfuchsin and decolorized with 20 per cent. sulphuric acid, on microscopic examination revealed, on an average, two tubercle bacilli each. The emulsion was mixed with an additional quantity of sterile, normal salt solution, so that each cubic centimeter of the dilution represented a strength equal to one drop of the original emulsion.

The blood obtained from the cow prior to her death, and the diluted emulsion made with the tuberculous mediastinal gland from her body, were used to inject seven groups of guinea-pigs, the records of which follow.

Group 1.—On April 24, 1909, eight guinea-pigs, Nos. 3626 to 3633 inclusive, received each an intra-abdominal injection of 3 c.c. of freshly drawn, warm blood. On May 6, 1909, guinea-pig 3627 died affected with congestion of the lungs. On autopsy no lesions of tuberculosis were found. On May 27 and 28, 1909, guinea-pigs Nos. 3626, 3628, 3629, 3630, 3631, 3632 and 3633 were killed and examined postmortem. No lesions of tuberculosis or other disease were found.

Group 2.—On April 24, 1909, eight guinea-pigs, Nos. 3642 to 3649 inclusive, received each an intra-abdominal injection of 3 c.c. of freshly drawn blood followed as quickly as possible by an intra-abdominal injection of 0.5 c.c. of tuberculous

emulsion. On April 30, 1909, guinea-pig 3642 died affected with inflammation of the large bowel. On May 27, 1909, guinea-pigs 3643, 3644, 3645, 3646, 3647, 3648 and 3649 were killed and examined postmortem. Every one of the seven guinea-pigs was found to be affected with generalized tuberculosis of the abdominal and thoracic organs.

Group 3.—On April 24, 1909, eight guinea-pigs, Nos. 3634 to 3641 inclusive, received each an intra-abdominal injection of freshly drawn, warm blood, followed as soon as possible by a subcutaneous injection into the right thigh of 0.5 c.c. of emulsion. On May 27, 1909, guinea-pigs 3636 and 3637, and on May 28, 1909, guinea-pigs 3634, 3635, 3638, 3639, 3640 and 3641 were killed and examined postmortem. The eight guinea-pigs all showed more or less extensive lesions of tuberculosis at the seat of the subcutaneous injection, tuberculosis of the adjacent, superficial inguinal gland, tuberculosis of the pelvic, lumbar and gastrohepatic glands and a sprinkling of tuberculous foci in the liver and spleen.

Group 4.—On April 24, 1909, eight guinea-pigs, Nos. 3658 to 3665 inclusive, received each an intra-abdominal injection of 3 c.c. of a mixture of defibrinated blood and tuberculous emulsion. Each 3 c.c. of this mixture was equivalent to 0.5 c.c. of the earlier described, diluted tuberculous emulsion. The mixture was two hours old at the time it was injected into the guinea-pigs. On April 25, 1909, guinea-pigs 3659, 3660 and 3661 died. The postmortem examination showed no lesions excepting a congested condition of the lungs and a quantity of unabsorbed blood in the peritoneal cavity. On May 12, 1909, guinea-pig 3662 died affected with congestion of the lungs; no lesions of tuberculosis were found. On May 27, 1909, guinea-pigs 3658, 3663, 3664 and 3665 were killed and examined postmortem. Three of the guinea-pigs were affected with completely generalized tuberculosis of the abdominal and thoracic organs and one, No. 3665, with generalized tuberculosis of the abdominal organs only.

Group 5.—On April 26, 1909, eight guinea-pigs, Nos. 3670 to 3677 inclusive, received each an intra-abdominal injection of 3 c.c. of the same mixture of blood and tuberculous emulsion used for the guinea-pigs of group 4. The mixture was forty-five hours old at the time it was injected into the guinea-pigs. On May 27, 1909, guinea-pigs 3670, 3671, 3672, 3673, 3674, 3675, 3676 and 3677 were killed and examined postmortem. Seven of the guinea-pigs were affected with generalized tuberculosis of the abdominal and thoracic organs and one, No. 3672, with generalized tuberculosis of the abdominal organs only.

Group 6.—On April 24, 1909, four guinea-pigs, Nos. 3650 to 3653 inclusive, received each an intra-abdominal injection of 0.5 c.c. of tuberculous emulsion. On May 6, 1909, guinea-pig 3651 died affected with congestion of the lungs. On May 27, 1909, guinea-pigs 3650, 3652 and 3653 were killed and examined postmortem. Guinea-pig 3650 showed tuberculous lesions of the spleen and omentum only and guinea-pigs 3652 and 3653 showed a fairly generalized tuberculosis of the abdominal and thoracic organs.

Group 7.—On April 24, 1909, four guinea-pigs, Nos. 3654 to 3657 inclusive, received each a subcutaneous injection, right thigh, of 0.5 c.c. of tuberculous emulsion. On May 27, 1909, guinea-pigs 3654, 3655, 3656 and 3657 were killed and examined postmortem. Guinea-pigs 3654 and 3656 showed each a small, tuberculous abscess at the seat of injection, a tuberculous condition of the superficial inguinal gland near the seat of injection and a fairly generalized tuberculosis of the pelvic and abdominal organs. Guinea-pigs 3655 and 3657 showed similar lesions, with the exception of abscesses at the seat of injection.

The guinea-pigs in the seven different groups were injected for the following purposes: Group 1, to serve as checks on the absence or presence of tubercle bacilli

in the blood of the tuberculous cow that was used for the investigation; Group 2, to show that the intra-abdominal injection of fresh, warm blood from a tuberculous cow can not protect against tubercle bacilli simultaneously introduced into the abdominal cavity; Group 3, to show that the intra-abdominal injections of fresh, warm blood from a tuberculous cow can not protect against tubercle bacilli introduced into other parts of the body than the abdominal cavity; Groups 4 and 5, to show that the blood of tuberculous cows has no special germicidal potency for tubercle bacilli; and Groups 6 and 7 to serve as guides relative to the amount of tuberculous disease to be expected in the bodies of the guinea-pigs that were injected with both blood and emulsion of tuberculous material.

The autopsy records of the guinea-pigs show, in a general way, very little difference between the animals that received only tuberculous emulsion and those that received both blood and emulsion. The guinea-pigs that received both blood and emulsion into their abdominal cavities showed numerically more extensive lesions of tuberculosis than the guinea-pigs that received only emulsion into their abdominal cavities. This condition would naturally be expected because the same number of tubercle bacilli contained in 3 c.c. of blood would be more widely separated and in better condition to start a large number of individual lesions than those in 0.5 c.c. of salt solution.

The total number of guinea-pigs injected in this supplemental investigation is 48, of which 8 received blood only, 32 both blood and tuberculous material and 8 tuberculous material only. Of the 32 that received both blood and tuberculous material and the 8 that received only tuberculous material, 6 guinea-pigs died prematurely and the remaining 34, when they were killed, thirty to thirty-one days after the injection, were all found to be affected with tuberculosis of a form that would have progressed to death in a short time.

Among the 8 guinea-pigs that received an injection of fresh warm blood without the addition of tuberculous material, 1 died prematurely and the remaining 7 were found on autopsy to be free from lesions of disease. As the cow that supplied the blood for the injections was affected, as her record shows, with extensive, advanced tuberculosis, the 7 guinea-pigs make a strong addition to the 88 parallel guinea-pigs of which the records are given in the article to which this supplement is attached, and hence we have 95 guinea-pigs as the total number that received injections of blood from tuberculous cattle into their peritoneal cavities, the most delicate test for tubercle bacilli available, and survived the injection long enough for tuberculosis to clearly manifest itself. Among this total of 95 guinea-pigs, not one case of tuberculosis developed.

The use of an emulsion of tuberculous tissue from the tuberculous cow that supplied the blood for the supplemental injections was preferred to the use of a pure culture of tubercle bacilli, because it seemed preferable to us to use infectious material and blood in this instance from the same individual case of tuberculosis.

The conclusion we draw from our work is this: If tubercle bacilli ever float in the circulating blood of tuberculous individuals, the occurrence is very rare, so rare indeed, that no form of tuberculosis can reasonably be characterized as a bacteriemia.[3]

Mohler examined the blood of 8 cattle microscopically and with blood from each of these cattle injected 5 guinea-pigs. The microscopic examinations and injections were made precisely in the manner described by Dr. Rosenberger. No tubercle bacilli were discovered microscopically and not one of the 40 injected

3. An independent investigation relative to the occurrence of tubercle bacilli in the circulating blood of cattle was made at the Federal Bureau of Animal Industry by Dr. John R. Mohler, Chief of the Division of Pathology.

guinea-pigs contracted tuberculosis. Two of the 8 cattle were in good condition, but were passing tubercle bacilli from their bowels; 2 of the cattle were in poor condition and were passing tubercle bacilli from their bowels; and 4 of the cattle were slaughtered for meat, but on inspection were found to be so extensively affected with tuberculosis that it was necessary to condemn and tank their carcasses under the federal meat inspection regulations.

This additional investigation is especially important because the methods used to discover tubercle bacilli in the blood were identical throughout with those used by Dr. Rosenberger, and which, in Rosenberger's work, invariably gave positive results.

THE RELAPSING FEVER OF PANAMA*

SAMUEL T. DARLING, M.D.
ANCON, CANAL ZONE

Publication of this paper has been withheld by the writer in order that the animal reactions of the new world monkeys might be worked out, and also that further attempts to produce a polyvalent hyperimmune serum might be made, but it is thought that the paper should now be published as it is, as the production of an immune serum can be much better accomplished near a constant and larger supply of laboratory animals.

INTRODUCTION

As Novy,[1] Mackie[2] and others,[3] in part, have pointed out, it is possible with the means at present at our disposal to separate the spirochetes causing relapsing fever into four groups, the separation being based on animal reactions, specific characters, such as agglutination and immunity, and certain clinical features of the infection in man.

This paper deals chiefly with some of the characters of the spirochete causing the relapsing fever of the Isthmus of Panama. The work was done at Ancon Hospital during the period between July, 1907, and February, 1908.

Relapsing fever has been reported from time to time in the canal zone since the American occupation in 1904. Most of the cases have been from Colon Hospital, about twenty-five in number, and five from Ancon Hospital (Panama). They have occurred chiefly among white laborers and have been distributed among Italians, Spaniards, Turks, Germans, Scotch, Greeks and Americans. The patients have all been seen in the wards, where the diagnosis has been made by blood examinations, and they have all presented the classical features of relapsing fever with two or more relapses.

---

*The greater portion of this investigation was read at the Canal Zone Medical Association, Ancon, C. Z., Feb. 8, 1908.

1. Novy, F. G., and Knapp, R. E.: Jour. Infect. Dis., 1906, iii, 291.
2. Mackie, F. P.: N. Y. Med. Jour., 1908, lxxxviii, 337.
3. Uhlenhuth and Haendel: Arb. a. d. k. Gsndhtsamte., 1907, xxvi, h. 1, 1.
   Manteufel: Arb. a. d. k. Gsndhtsamte., xxvii, h. 2, 327.
   Shellack, C.: Arb. a. d. k. Gsndhtsamte., xxvii, h. 2, 364.
   Marchoux, E., and Salimbeni, A.: Ann. de l'Inst. Pasteur, 1903, xvii, 569.

Carlisle[4] has given us an excellent summary of the geographical distribution of relapsing fever. With regard to America, a few sporadic cases and one epidemic have been reported in the United States, all of them being traced to recently arrived immigrants or sailors. Cases have been reported from Tuxpam, Mexico, a seaport between Vera Cruz and Tampico, and from Cuba, Peru, Chile and Bolivia. Hirsch[5] in 1881 stated that nothing was known of its existence in Central and South America. Dr. R. Franco[6] of Bogota, U. S. of Colombia, has discovered a febrile spirochetosis, the spirochete of which, it is said, can not be differentiated from *Sp. duttoni*. *Ornithodoros turichatus* is thought to be the species of tick which conveys the disease. It may be that the relapsing fever of Panama has been introduced from the United States of Colombia, where it appears to be endemic.

There are no records of the disease having been recognized on the Isthmus of Panama previous to 1905. If it appeared here before that date it was probably called "malarial fever" or "typhus fever." In the absence of an absolute diagnostic criterion many cases of relapsing fever in the past must have been confounded with typhus and malarial fevers.

It would be disappointing to find in a disease of so wide a geographical distribution as relapsing fever that Hippocrates[7] had not made some clinical observations, and we are, therefore, not surprised to learn of an epidemic occurring in the island of Thasus, off the coast of Thrace, described by Hippocrates, presenting many features of resemblance to relapsing fever. "The chief points of resemblance between the ancient and modern epidemics are the invariable occurrence of relapses, the marked character of the crises, and the frequent associations with the more ordinary events of the disease of copious perspirations, hemorrhages, particularly epistaxis, jaundice and splenic enlargements."[8]

From Carlisle's summary of the various reported epidemics and sporadic cases we learn that at one period relapsing fever was regarded as being indigenous to the British Isles. J. Warburton Begbie[8] gave as a synonym the term "epidemic fever of Scotland or Ireland."

4. Carlisle, R. J.: Jour. Infect. Dis., 1906, iii, 233.

5. Hirsch, A. (see Carlisle): Handbook of Geographical and Histological Pathology, i, London, 1883.

6. Blanchard, R.: Bull. Acad. Med., 1907, 5111. Abstr. in Jour. Trop. Med. and Hyg., 1908, xi, 58.

7. Hippocrates: Epidemiorum Hippocratis, Liber Primus, Sectio Secunda, Status Tertius.

8. Begbie, J. W.: Reynolds' System of Medicine, Lippincott, Philadelphia, edition 2, i, 456.

Relapsing fever has frequently been associated with typhus fever and with the insanitary conditions which favor the development of typhus fever. It was recognized in Scotland and Ireland as early as 1817 and after several epidemics was last seen there in 1871. The cases in the United States reported by Austin Flint occurred in 1850-51. Clymer at Philadelphia in 1844 recognized it among Irish immigrants there. It was at this time that relapsing fever was very prevalent in the British Islands, particularly at Edinburgh. The disease in the United States did not spread very far. A few cases occurred in Washington, Maryland, New Jersey and Connecticut. One case was noted in Boston. Flint's cases were observed in Buffalo, where he was practicing at that time. Philadelphia and New York City were visited by an epidemic in 1869.

There have been numerous epidemics in Europe, occurring in Russia for the first time in 1833 at Odessa, a seaport. There have been epidemics in St. Petersburg, Warsaw, Moscow, Novgorod and many other places in Russia. The United States Consul-General's office reports the total number of deaths in Russia from relapsing fever in 1901 as given by the Medical Department to be 2,466 out of a total of over 700,000 deaths from infectious diseases.

Many cases have been reported from India. H. Vandyke Carter[9] thought that relapsing fever was constantly present in Bombay.

Germany has been visited by epidemics from time to time. Obermeier[10] made his observations on relapsing fever during the epidemic of 1868-73 in Berlin. Germany has been free from an epidemic since 1880. One imported case was discovered in Hamburg in the person of a Persian emigrant on his way to the United States. In spite of the emigration from Russia at present and from Great Britain and Ireland in the past when epidemics of relapsing fever were present, it is to be noted that the disease has never gained a foothold in the United States. Relapsing fever patients are infectious for a very long period, four to seven weeks, throughout the entire course of the disease, giving a suctorial insect or acarid abundant opportunities to take on the spirochete, so that its failure to spread when introduced is strongly indicative that the conditions are unsuitable for the continued existence of the intermediary or alternate hosts—insects, acarid or rat.

The spread of relapsing fever during the past century may be related to the distribution of *Mus decumanus* over Europe and around the world.

9. Carter, H. V.: Spirillum Fever, London, 1882.
10. Obermeier, O.: Centralbl. f. d. med. Wissensch., 1873, p. 145.

From a study of the epidemiology of relapsing fever we would expect to find cases appear in seaport towns and those in the interior reached by emigrants or sailors from places where relapsing fever was endemic.

Thirty-one cases of relapsing fever have been recognized in the Commission hospitals in the canal zone during three years out of about 65,000 admissions, where blood examinations are made of every patient entering the medical wards. The disease here has not been confined to one race or nationality.

Table 1 records certain clinical data of interest in connection with seventeen cases occurring during 1907:

TABLE 1.—CLINICAL DATA IN 17 CASES

Whites (15)	
Americans	4
Germans	2
Spaniards	4
Scotch	2
Italians	1
Greek	1
Turk	1
Blacks (2)	
Martiniquan	1
Antiguan	1

Ages		Length of Residence on the Isthmus (2 months to 3 years)	
13 years	1	2 months	1
21 years	1	3 months	4
22 years	1	4 months	1
26 years	1	4½ months	1
27 years	3	5 months	1
30 years	2	6 months	1
32 years	2	6½ months	2
35 years	1	7 months	1
36 years	1	11 months	1
39 years	1	15 months	1
40 years	1	24 months	1
44 years	1	30 months	1
45 years	1	36 months	1

Occupations		Place of Residence on the Isthmus	
Laborers	11	Colon and Cristobal	5
Carpenters	2	Rio Grande	1
Cable operator	1	Ancon dredge (suction)	1
Sailor (dredge)	1	Gatun	7
Engineer	1	Empire	1
Unknown	1	Mindi	1
		Corozal	1

It is to be noted in Table 1 that there is a disproportionate number of cases among white employés—7 to 1—while the number of white to negro employés during the period from which the data was compiled was more nearly 2 to 7. The average number of white employés for the year 1907 was 10,709, while the average number of black employés for the same period was 28,634. The seventeen cases tabulated were distributed among natives of nine countries, who had lived on the isthmus from two to thirty-six months; thirteen of the seventeen patients, in all probability, developed the disease on the Atlantic or Colon side of the isthmus, where there appear to be two foci of infection, Colon and Gatun, the former a seaport and the latter a village six miles from Colon on the Pan-

ama railroad, on the site of the proposed locks, where a large number of laborers are quartered.

It is not intended to discuss, at any length, the clinical aspects of relapsing fever, but, more particularly, to give an account of some observations which it is hoped will throw some light on the nature of the micro-organism causing the fever found on the Isthmus of Panama.

Attempts to identify the spirochete of relapsing fever by means of morphological and staining characters are subject to grave inaccuracies, for there is a fairly wide limit to the variations of length, width, number of spirals, regularity of curvature and homogeneity in the same strain in different animals of the same species and at different periods during the infection.

The terms "spirillum" and spirochete" are used at present indiscriminately when applied to the micro-organism causing relapsing fever. With high magnification and better methods of staining and cultivation it may be possible to classify the spiral-shaped micro-organism in groups according to size, the number and arrangement of flagella; according to their shape—cylindrical or ribbon-shaped; according to their pathogenicity, according to their amenability to culture.

Spirochetes are almost as widespread as bacteria. In the blood stream they are associated with relapsing fever in men and the spirillosis of geese, goats, horses, rats, mice, fowl, sheep, cows and bats. Spirochetes have been found in non-specific ulcers on the external genitalia, ulcers on the legs or body, tropical ulcers, in stomatitis and in intestinal inflammation and ulceration. They have been found at autopsy here in Panama in most cases of gangrene of the lung and in other lesions of the respiratory tract. In a case of sprue, recently, smears from a parchment-like membrane at the margin of the teeth showed a pure culture of spirochetes and fusiform bacilli. Spirochetes are practically always found in inflammatory conditions of the mouth, particularly of the gums. It is not uncommon to find spirochetes associated with protozoa in infections of the intestinal tract of man and the lower animals.

Insects harbor spirochetes, which have been found in their intestinal tract, sexual organs and ova. Several varieties of spirochetes are found in natural waters, particularly in the surface pollicles of stagnant waters.

Schaudinn[11] directed the attention of the medical world to a group of spiral-shaped micro-organisms, more especially to one member of the group which he has designated *Treponema pallidum*, and with Hoff-

11. Schaudinn, F., and Hoffmann, E.: Gsndhtsamte., 1905, xxii, 527.

mann, in 1905, has shown to be almost constantly present in the tissues of persons suffering from syphilis. The same year Castellani[12] described the spirochetes found in yaws.

The spirochete of relapsing fever was discovered by Obermeier in 1873, who observed it for the first time in 1868 while studying an epidemic of relapsing fever in Berlin. Obermeier's observations were made with the spirochete of European relapsing fever, a disease belonging to the general class of relapsing fevers, but one which must be differentiated from the tick-fever of Africa and the fevers of Bombay and the Isthmus of Panama.

It is impossible at the present time to differentiate the varieties of spirochetes of recurrent fever by cultural methods, and it can not be said that morphology affords an accurate means of distinguishing them, for in the observations on the isthmian relapsing fever the spirochete has exhibited considerable variation in size, length, number of spirals and in staining qualities. It will be necessary then to adopt as a means of differentiation the effects of the micro-organism on man and susceptible animals—animal reactions and the effect of the serums and cells of susceptible animals on the micro-organism—agglutination, lysis and phagocytosis.

H. Vandyke Carter published some notes in 1877 and a complete description in 1882 of the spirillum fever of Bombay. The disease appeared in Bombay in 1877, being introduced by immigrants from famine districts. Carter successfully inoculated monkeys with the spirochete of Bombay fever. Rogers'[13] description of the epidemic is very much like that of Welsh[14] of an early epidemic in Scotland, the disease spreading through families and attacking clinical clerks and hospital attendants. According to Norman Chevers and Carter, relapsing fever has always existed in India. During periods of famine the mortality has been very high. It is to be noted that vermin are particularly active in debilitated persons.

Human tick-fever, or the relapsing fever of the Congo, was first observed by Livingstone[16] in 1857. The etiologic factor, *Sp. duttoni*,

12. Castellani, A.: Jour. Ceylon Brit. Med. Assn., 1905, ii, 54.

13. Rogers, L.: Fevers in the Tropics, London, 1908, Oxford Med. Publication: Henry Frowde.

14. Welsh, B.: A practical treatise on the efficacy of blood-letting, etc., Edinburgh, 1819.

16. Livingstone: Missionary Travels and Researches. John Murray, London, 1857. Chapters xix, pp. 283, 382; xxx, pp. 628, 629.

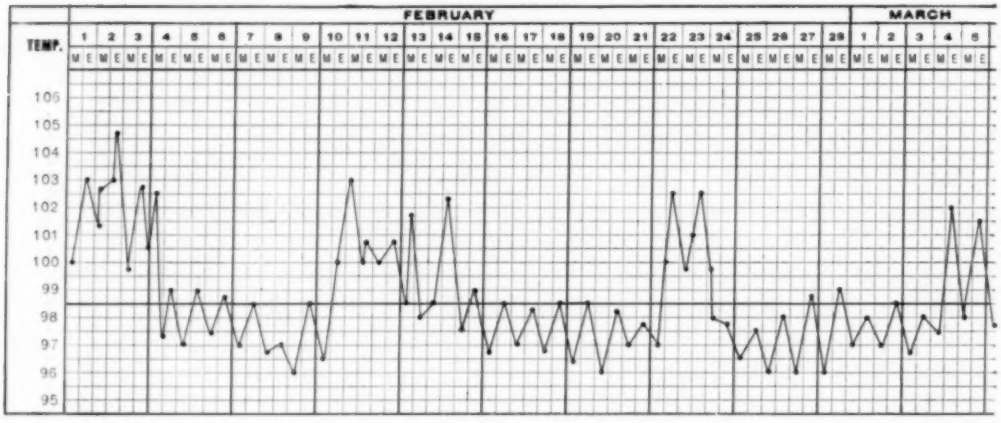
The spirochetes of relapsing fever may be placed in four groups:

Group A.—The group causing a relapsing or recurring infection in man, monkeys, white mice and white rats, including *Sp. duttoni* and the tick-fever of Africa.

Group B.—The group causing a recurring infection in man, monkeys and white mice, but with a single paroxysm in white rats. This group comprises the relapsing fever of Panama and the two cases studied by Carlisle.

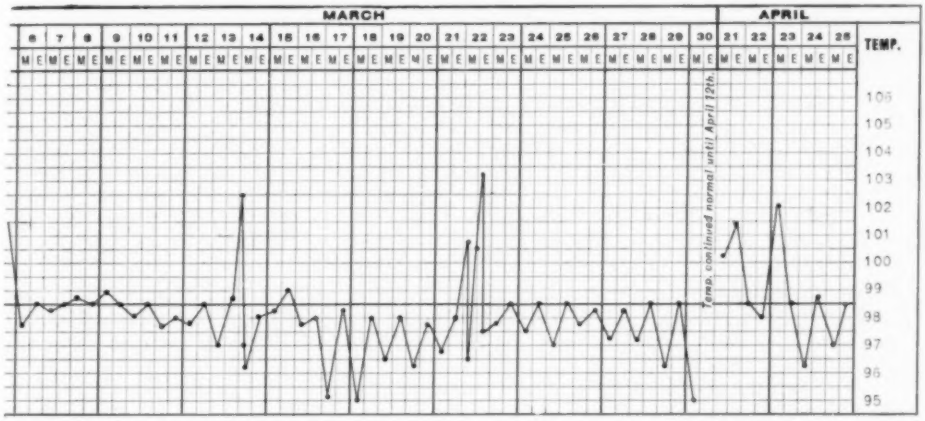
Group C.—The group causing a recurring infection in man and monkeys but failing to cause an infection in small rodents with blood direct from human sources, yet causing an infection in small rodents after a preliminary passage through the monkey. This group includes the relapsing fever of Europe, caused by *Sp. obermeieri.*

Group D.—The group causing a recurring infection in man and monkeys but only transient infections in white rats and white mice. This group includes the relapsing fever of Bombay caused by *Sp. carteri.*


FEBRUARY
MARCH
TEMP.
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 1 2 3 4 5
M E M E M E

Furthermore, as has been determined in this investigation, there is an individuality to the strains of spirochetes of the same species in the same locality, for an animal immunized to one strain is not immune to another strain from a different human source.[22]

In this investigation of the relapsing fever of Panama the animal reactions of white mice, white and wild rats and monkeys have been worked out. Experiments in immunity have been carried out, parallel infections with *Trypanosoma lewisi* have been studied, and the part played by the liver in the infection has been inquired into. The specific nature of stains has been investigated, and the effect of certain anilin dyes in lowering the resistance of inoculated animals to the infection has been noted.



the paroxysm and the subnormal oscillations of temperature during the afebrile period.

SOURCE OF THE SPIROCHETES USED IN THIS WORK

Animals have been inoculated from four patients, but only two of the strains so derived have been carried on for any length of time. The two strains used in this investigation will be designated as A and B.

ORIGIN OF STRAIN A

Patient.—L. G., hospital No. 33,107, from whom this strain was obtained, was a laborer, native of Spain, aged 39; length of residence on the Isthmus, three years; residence Gatun, a village in the Canal Zone, six miles from Colon, and one of the foci of infection. (See Fig. 3.)

22. I have since learned that Carl Fränkel (abstr. in Jour. Trop. Med. and Hyg., 1908, xi, 70, from Klin. Med., 1907, p. 928) has made a similar observation with regard to the spirochetes of the African fever.

Previous History.—The patient was twice in hospital; two weeks in Colon hospital and two weeks in Ancon hospital. He had not taken quinin.

Present Illness.—He has been ill four days. Onset with chill followed by fever, since when he has had several chills and much fever.

Clinical Notes (By D. Summersgill).—The spleen was enlarged and tender; lungs, glands, liver, skin, blood vessels, nervous system, urine and stool negative. The blood contained a few spirochetes. Blood was taken for animal inoculation Oct. 11, 1907, at 3:30 p. m., when the temperature was 102 F. Spirochetes were present in the peripheral blood at this time. Four cubic centimeters of blood from vein at elbow were inoculated intraperitoneally into a small monkey *cebus* and 2 c.c. intraperitoneally in two white rats and two white mice.

ORIGIN OF STRAIN B

Patient.—B. J. (See Fig. 4), from whom this strain was obtained, was a patient in Colon hospital; laborer, native of Turkey; age 27; residence, Gatun; length of residence on the Isthmus, six and one-half months.

Previous History.—The patient had been in hospital once; had had malaria many times; no dysentery.

Present Illness.—He had been sick three months; had swelling of feet with ulceration, and weakness.

Physical Examination (By Dr. Brem).—Abdomen pendulous. Movable flatness in flank—indistinct fluid. Mucosæ pale. Liver enlarged. Skin waxy. Tongue pale, flabby and coated. Lungs and glands negative. Spleen palpable 9 cm. below costal margin. Blood vessels soft. Pulse full. Heart: Presystolic murmur prolonged into systole, blowing and coarse, heard all over precordium with maximum intensity at apex; pause in aortic and pulmonary area; transmitted into vessels of neck, to axilla and towards sternum along costal margin. Feb. 5, 1908: Apex beat not visible. Palpable in the fourth and third interspaces, 12 cm. to the left of the sternum. Soft bruit accompanying the first sound all over precordium. Best at apex. Blood pressure 116.

Leucocytes, Jan. 21, 1908, 4,500; Jan. 22, 1908, 6,000.

Red blood cells, Feb. 3, 1908, 4,800,000; red blood cells, Jan. 8, 1908, 3,344,000.

Hemoglobin, Jan. 15, 1908, 70 to 75 per cent.; Jan. 16, 1908, 55 per cent.; Feb. 2, 1908, 69 per cent.

Urine and stools, negative.

Blood taken from patient's arm Jan. 21, 1908, and inoculated into two white rats intraperitoneally.

CHARACTERISTICS OF THE MICRO-ORGANISM

In human blood, in the relapsing fever of Panama, there are comparatively very few spirochetes seen during the paroxysm, one to forty or fifty fields, or perhaps only three or four to a cover-slip. In the period between paroxysms it is rarely possible to find a spirochete in the peripheral blood. In none of the cases studied here has the spirochete been present in what might be called considerable numbers. This observation is another means of differentiating the fever of Panama from that of Europe. Blood films taken from cases of the relapsing fever of Europe often show considerable numbers of spirochetes. Films from a case of European relapsing fever (Fig. 2), which I have studied through the kindness of Dr. Samuel J. Goldfarb, often show six spirochetes to

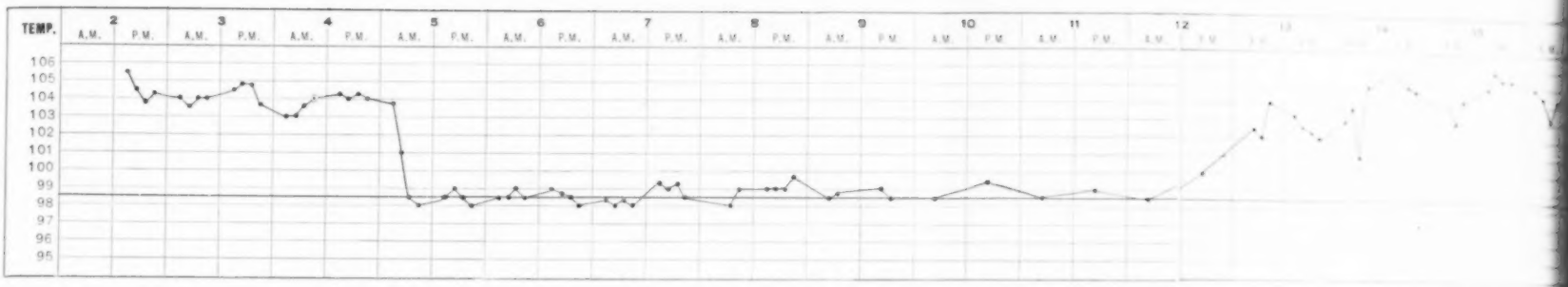


Fig. 2.—Course of case of relapsing fever of Europe. Note the sustained temperature during the paroxysm and the prole

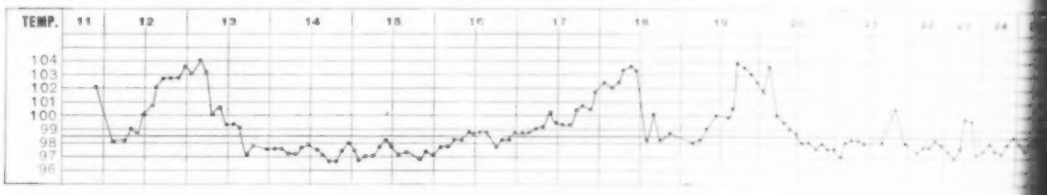


Fig. 3.—Course of case of relapsing fever of Panama from which strain A was obtained.

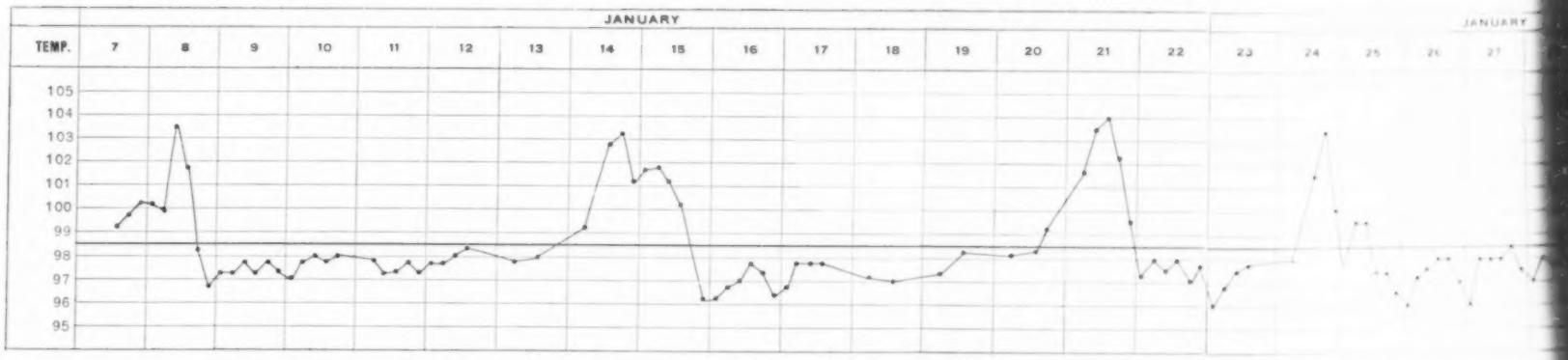
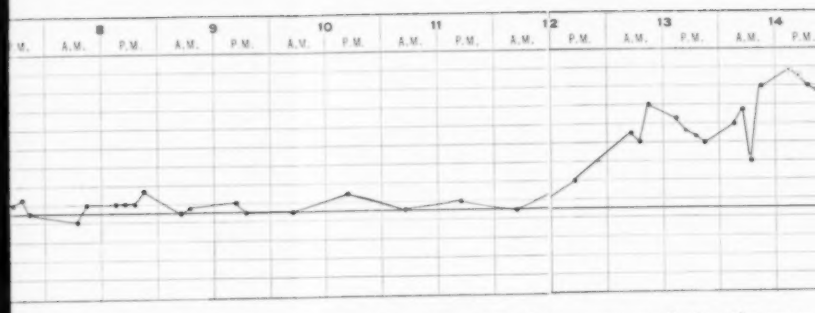


Fig. 4.—Course of case of relapsing fever of Panama from which strain B was obtained.



e of case of relapsing fever of Europe. Note the sustained temperature during the parox

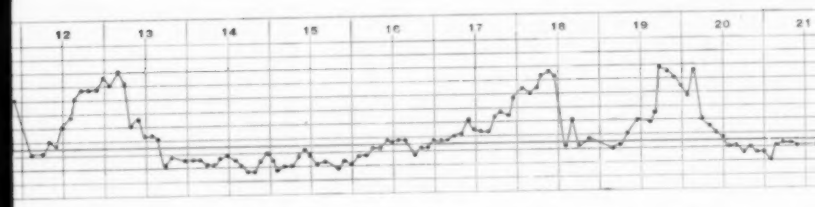


Fig. 3.—Course of case of relapsing fever of Panama from which strain

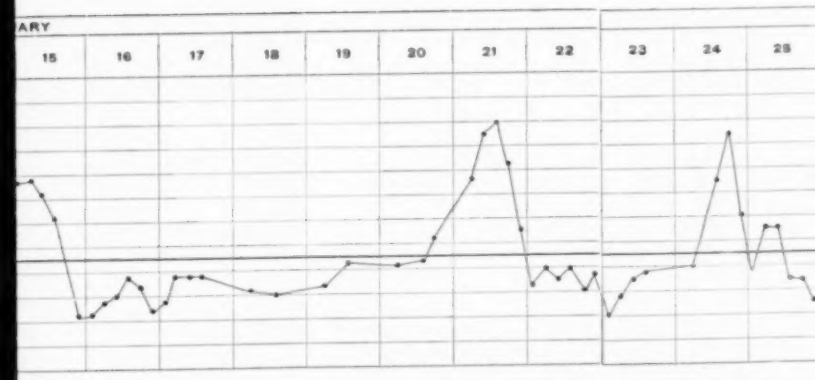
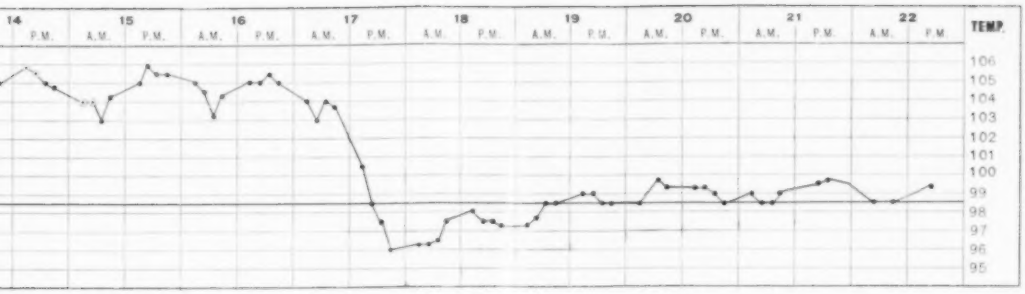
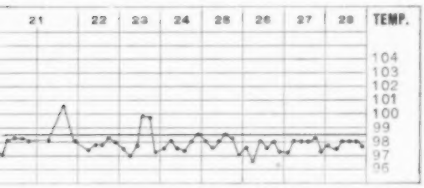


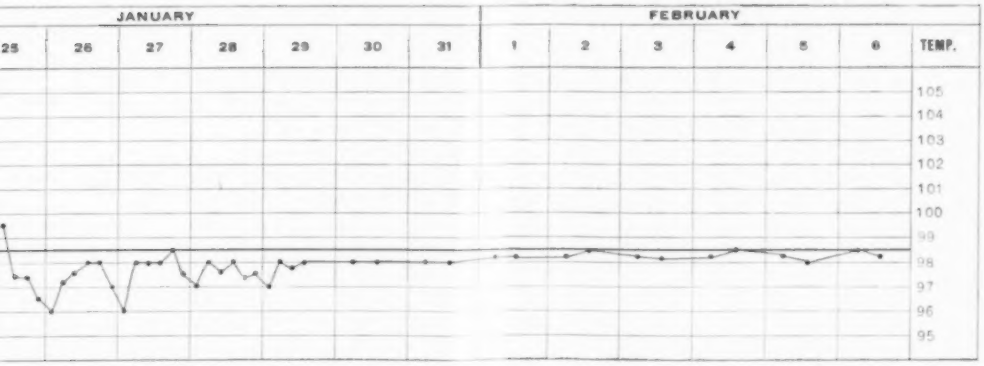
Fig. 4.—Course of case of relapsing fever of Panama from which strain



paroxysm and the prolonged duration of the same.



rain A was obtained.



ain B was obtained.

one oil immersion field. Such a picture is never seen in blood films from cases of the fever met with here.

The description of the spirochetes is based on observations made with richly infected blood of white mice and white rats.

MORPHOLOGY

The movements of the spirochete are very rapid, except just before its disappearance from the blood stream. At this time observations of the nature and character of the movements may be made, or the motions may be slowed down by treating a drop of blood with two or three drops of citrated saline solution and making a cover-slip preparation. At first the motion of the spirochete is violent; in two or three hours it can be made out with great ease. Red blood corpuscles become segregated and in the clear spaces spirochetes will have gathered and can be seen moving

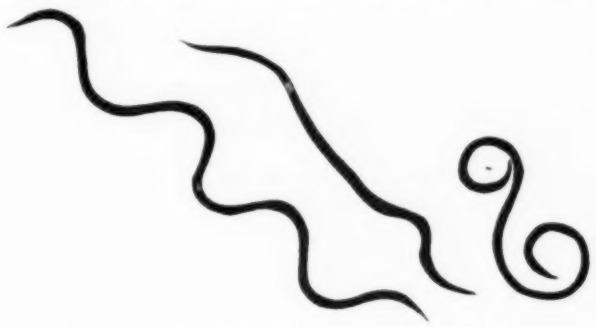


Fig. 5.—Spirochetes from blood of Rat 31, seen at height of the infection, showing one normal double form A, one stretched out form B, and one recurved form C, in one cover slip preparation.

in various directions. Frequently a spirochete may be seen to be attached to a red blood corpuscle by an invisible flagellum; the margin of the red blood corpuscle then becomes pulled out and the whole cell distorted, even dragged away down-stream with a spirochete evidently attached, yet always keeping nearly a red cell's diameter away. When the red cell is fixed, the attached spirochete may be seen to rotate to the right, apparently trying to go forward, then after a pause the rotatory movement is apparently reversed; this reversed movement frequently carries the spirochete away from the red blood corpuscle a short distance, though it still remains attached to it. During the pause in the rotation there is an opportunity to observe its outline and to determine whether the spirochete

is a spiral cylinder or ribbon. This question is difficult to determine when the spirochete is met in cross-section. During the pause just mentioned some spirochetes appeared to be spiral ribbons. One appeared to be curved in one plane only—on the flat. In fresh citrated blood preparations the observations were made with artificial light, Zeiss 2 and 3 mm. objectives and 6, 8, 12 and 18 oculars. Under these conditions, while the various motions of the spirochetes were made out with ease, the impression received as to the topography of the spirochete was probably illusory. Any one who has watched the polished balls on the governor of a stationary engine, when illuminated by artificial light, knows how by a slight effort of the will the balls may be seen to rotate to the right or to the left; just so with the spirochetes. One is not absolutely sure that it is rotating to the right or to the left, but one feels sure that it is rotating. Perhaps the physicists may throw some light on this matter by telling us what the optical effect on the observer will be under, say, two hypothetical conditions: light from an incandescent lamp reflected by a mirror through substage condenser, glass slide, blood serum, through the transparent body of a spirochete having a refractive index of $1 + x$ and a diameter of 0.3 micron under the following conditions: (a) the body of the spirochete rotating in a plane transverse to the rays of light, the body being a spiral ribbon; (b) the body being a spiral cylinder. I believe the question involved insoluble by a mere inspection of fresh or stained specimens.

At the end of three hours in citrated preparations the spirochetes frequently appeared attached to a red blood corpuscle at one end. The movements of the attached spirochete cause the red blood corpuscle to change its outline to a very marked degree, frequently pulling it out into a pear-shaped body. The spirals or curves of the spirochete push and pull the red blood corpuscles out of contour, giving one the impression that the spirochete is possessed of great rigidity.

Besides the rotary movement, there is an undulating movement or tremor; the spirochete does not always move rapidly away from the field, but rather rotates and trembles in one spot and then darts off a short distance within the field.

In citrated blood preparations, at the height of an infection many spirochetes may be seen in a prefragmenting stage; their motion is slow and there is a tendency to wreath or ring formation, their two extremities becoming attached and they may be seen to shake and tremble, the body of the spirochete apparently breaking up, while the fragments are apparently held in apposition by a sheath or envelope. The effect is very much like that of an agitated chain.

In citrated blood preparations, the spirochetes, after a short time, are commonly found in the clear spaces formed by the segregation of the red blood corpuscles.

The undiluted fresh blood preparation at room temperature, 76 to 82 F., presented on one occasion, at the end of sixteen hours, about the same picture that the citrated blood did at the end of four hours.

Aerotactism, such as is observed in fresh water flagellates, was never noticed. Aerotactism refers to the air-hunger observed in water flagellates from surface pellicles when studied in cover-slip films. These protozoa may be found in large numbers close to the margin of air bubbles.

Agglutination is seen in fresh preparations at the height of an infection; the parasites may adhere to one another end to end or side by side; the bodies of the spirochetes are probably fastened by entangled flagella.

When fresh and stained preparations are made from the same drop of blood, the fresh specimen frequently shows all regular forms, while

Fig. 6.—Blood from Mouse 8. The clear space in the middle is suggestive of transverse fission and the loop is suggestive of longitudinal fission.

the stained specimen may contain many bodies curved or straightened out. Drying and staining processes, therefore, may alter the regularity of contour of the spirochetes.

In stained preparations, the length, contour, number of spirals, the presence of flagella and staining qualities of the spirochetes were noted. Great variation in the regularity and number of curves was noted. In one film coarsely and finely curved forms were seen, as well as coarse and fine curves in one organism. Irregular curvatures, straightened and recurved forms were frequently encountered.

Toward the end of an infection achromatic spaces in the spirochete, or the prefragmenting phase, were frequently seen; sometimes as many as four spaces could be counted in one spirochete, the length of which was 8 or 10 microns. These achromatic spaces are not to be confounded with the achromatic space which is present in the double forms, which

appears just before transverse fission, and is always centrally located and wider than the former.

The act of subdivision was not observed. The centrally located achromatic space in the double form is strongly suggestive of transverse fission, while a very few loop forms with an apparent longitudinal split were suggestive of longitudinal fission. The achromatic zones are well demonstrated in films stained with acetone gentian violet. In these preparations, curiously, there is never the least semblance of a periplast, while in the films stained with some modification of the Romanowsky stain a faint line, bridging over the achromatic zone, is noted. Some films which were stained with Muir's flagellum stain showed spirochetes with a single, terminal, faintly staining flagellum, its diameter decreasing toward its free extremity. Occasionally, in a film stained with acetone gentian violet, a ring form could be seen. In these instances, in which the free extremity of a flagellum was in relation with the opposite end of the spirochete, a little more than one-third

Fig. 7.—Spirochete from blood of Rat 66, showing large and small curves in one individual.

of the circumference of the ring would be more faintly stained than the rest and tapering, corresponding to a flagellum. In several of the acetone gentian violet preparations the appearance of spiral ribbons seemed unmistakable. In double infections of spirochetes and trypanosomes films were stained in various ways; yet, whenever the chromatin filament of the trypanosome was in evidence, nothing at all like this structure could be made out in the spirochetes. *A priori*, why should the spirochete of relapsing fever be provided with a chromatin filament? The spirochete is a rigid spiral, staining homogeneously, in every way like a bacterium, never like a protozoon. Its peculiar motion is probably due to rotation caused by a lashing contracting movement of the flagellum inducing a rotation of the body of the spirochete, the rotation being favored by its flat or ribbon-shaped contour. Its body is rigid and not flexuous to the degree observed in trypanosomes. The spirochete stains homogeneously, except just before its disappearance from the peripheral blood, when achromatic spaces or zones appear—the presegmenting

phase. It is stained purple with polychrome blues as bacilli are. Blue vacuolated cytoplasm with chromatin granules, such as one sees in protozoa, is never noticed, and it is decolorized by Gram's method. A very striking characteristic of spirochetes stained by gentian violet is the decolorization of the spirochete, either at once or after a few days, on exposure to diffuse sunlight. Films from Rat 31 colored with acetone gentian violet stained intensely and showed the achromatic zones beautifully. A few days later the spirochetes were completely decolorized and could be made out only by their sinuous transparent bodies; the red blood corpuscles and leucocytes, however, retained the gentian violet perfectly. A similar result was observed whenever a film was stained with Muir's too old flagellum stain, even when it had been previously stained with a polychrome blue stain.

SIZE

Measurements of length were made from stained preparations of the blood of rats and mice. Single spirochetes in which no achromatic zone could be detected measured from 7.2 to 13.2 microns. Double spirochetes having a central achromatic zone measured from 13.2 to 17 microns. The number of complete S-forms in single spirochetes having no achromatic zone varied considerably in the same film. The above measurements were made from spirochetes seen in the blood of Mouse 1, at the first remove from man.

ANIMAL REACTIONS

In man the disease is characterized by recurring paroxysms of fever lasting, usually, from twenty-four to forty-eight hours. The temperature rises slowly or rapidly to 103 or 104 F., occasionally to 105 F. There is always a chill and the access can not be distinguished by inspection from a malarial paroxysm. The duration of the first paroxysm is not definitely known, but is probably three days. The temperature falls slowly or suddenly to normal with the subsidence of symptoms, when, after a period of from three to eight days, oftenest five or six days, there is another paroxysm resembling the first and lasting about the same length of time. The usual number of paroxysms is three. There may be abortive paroxysms in which the temperature rises a degree or two above normal for two or three hours. During the febrile paroxysms a a few spirochetes appear in the peripheral blood. Very rarely a spirochete may be detected during the afebrile period. The spleen is always enlarged and tender; the tongue, pale and coated. Epistaxis occurs occasionally during febrile paroxysm (during the first relapse in case of F. S.). The pulse and respirations are accelerated during the febrile

paroxysm. Ten or twelve hours after the drop in temperature there is profuse sweating. Several cases were complicated by diarrhea and colitis with pus and blood in the stools. There have been no deaths in uncomplicated cases.

ANIMAL REACTIONS: WHITE MICE

Among animals the white mouse is the most susceptible. Mouse 3 was infected with blood containing not more than one or two spirochetes. As it was found that a drop or two of infected mouse-blood was sufficient to infect another mouse, and as it was desired to observe the progress of the disease without unnecessary sacrifice of the limited number of animals at my disposal, blood from the tail of an infected mouse was expressed into a Petri dish containing citrated saline solution to prevent clotting; this was injected into the peritoneal cavity of the next mouse in the series. Fifteen mice were infected in this way.

The disease in white mice is very much like that in man. There were three paroxysms, during which spirochetes appeared in the peripheral blood. The temperature of the smaller animals was not taken on account of the wide normal daily variation and the influence of various undetermined factors in causing irregularities in the temperature curve and making its record valueless. The temperature of the larger animals—goats, monkeys and dogs—was found to vary similarly.

The number of paroxysms, number of spirochetes in the blood and the period of incubation depend on a number of factors. The period of incubation by the method of inoculation used varied from twenty-four hours to six days. Mouse 3, inoculated from Mouse 1 with five drops of tail blood containing one spirochete to 500 fields, showed one spirochete in 100 fields after a period of twenty-four hours. Mouse 13 was inoculated from Mouse 12, when the blood from No. 12 showed no spirochetes in 500 fields. The period of incubation in No. 13 was five days and the infection was a typical one with three paroxysms.

Mouse 1 was inoculated directly from the patient during his second paroxysm. No spirochetes were seen until the third day, when there were two to a field. Two c.c. of uncitrated blood were used to infect Mouse 1. The infection was unusual, inasmuch as the period of incubation, in spite of the large amount of blood used, was prolonged, yet the spirochetes remained constantly in the animal's blood, without intermission, for ten days, when death occurred. Continuous infections have been observed in two animals, a white mouse and a black rat. The issue was fatal in each case. During the course of the infection in Mouse 1 there was a high degree of polychromatophilia, basophilic granular degeneration of the red blood cells, leucocytosis and a marked diminution in the number of red blood cells. Dyspnea and convulsions occurred before death. At autopsy the spleen was greatly enlarged and there were two encysted larval tapeworms (*Echinococcus murinum*) in the liver. The day before death spirochetes were rapidly increasing in the peripheral blood, there being 10 per field, with considerable agglutination. The mouse, therefore, died at the end of a paroxysm. (See chart of Mouse 1, Fig. 8.)

Mouse 2, inoculated intraperitoneally with 2 c.c. uncitrated blood directly from patient, had five and possibly six paroxysms with recovery. There was a marked remission during the first paroxysm, and as the blood was not examined on October 15 it is not known whether spirochetes were absent on that day or not. (See chart of Mouse 2, Fig. 8.)

Mouse 3, inoculated from Mouse 1, had a period of incubation of twenty-four hours and four paroxysms.

Mouse 4, inoculated from Mouse 2, had a period of incubation of forty-eight hours, only two paroxysms, and died six days after the disappearance of spirochetes from the peripheral blood. At autopsy the spleen was not much enlarged, and spirochetes were absent from the peripheral blood. During the progress of the infection there was much polychromatophilia and basophilic granular degeneration of the red blood cells. This basophilic granular degeneration has probably been mistaken for the resting forms of spirochetes. (See chart of Mouse 4, Fig. 8.)

Mouse 6, inoculated from Mouse 1, had three paroxysms and died three days after the disappearance of spirochetes from the peripheral blood. (See chart of Mouse 6, Fig. 8.

Mouse 9, inoculated from Mouse 3, had a period of incubation of 48 hours, two paroxysms, and was accidentally killed thirteen days after second and last paroxysm, during which period paroxysms were absent from the peripheral blood. (See chart of Mouse 9, Fig. 8.)

Mouse 12, inoculated from Mouse 6, had a period of incubation of forty-eight hours and three paroxysms, while spirochetes remained absent thirteen days after the last paroxysm. (See chart of Mouse 12, Fig. 8.)

The amount of blood used to inoculate these animals was about five drops. This was caught in a sterile Petri dish containing 5 c.c. of sterile, citrated, normal saline solution, and injected immediately intraperitoneally.

The spirochete counts were made from smears on cover-slips stained with Leishman's or Hasting's stain. A field was that which was obtained by a Zeiss 2 mm. objective and No. 6 ocular. When spirochetes were sparse at least 300 fields were counted; frequently 500 or a thousand; sometimes, three or four films.

It will be noted that in the initial paroxysm there is a greater number of spirochetes per field per day and the duration of the paroxysm is somewhat longer than the subsequent ones. The first paroxysm lasts about three days. The period between the first and second paroxysm is from four to five days. The second paroxysm lasts from two to three days; this may be followed by an intermission of four or five days, and followed by a third relapse lasting one, two or three days.

In severe infections the period of intermission between relapses may be shortened to one day. During the relapses the mice are slightly indisposed and take little food. After taking the blood films or removing blood for inoculation the tails of some infected mice bled profusely and required an application of collodion.

Mouse 1 lost considerable blood, which probably helped to cause some of the blood changes noted above and may have influenced the character of the infection and the fatal issue.

Fig. 8.—Chart of group paroxysms in white mice showing the numbers of spirochetes in the peripheral blood. Circles (○) specify no spirochetes in 300 or more fields; crosses (×), blood not examined on this day.

Of the deaths in mice all but two occurred several days after spirochetes had disappeared from the peripheral blood. One of these had, in addition to the heaviest infection noticed in mice, a profound anemia. Most of the dead mice had encysted larval tapeworms (*Echinococcus murinum*) in the liver.

An attempt was made to ascertain if there was a definite or constant periodicity in the relapses which might be correlated with a life cycle of the parasite, the period of which might be suggested if the paroxysms appeared on similar days in the original animals and in those subinoculated from them; there was, however, no conformity between such paroxysms. (See Fig. 8, chart of group paroxysms.)

ANIMAL REACTIONS; WHITE RATS

The infection in white rats is characterized by a single paroxysm lasting two or three days followed by the rapid disappearance of spirochetes from the blood stream. The disappearance is not complete, as will be shown later, but it is rarely possible to demonstrate spirochetes in the peripheral blood twenty-four hours after the height of the infection.

The period of incubation in white rats depends on the number of spirochetes injected, among other factors. When minimal amounts of tail blood are injected the period of incubation is from two to five days. When larger amounts of heart's blood are used spirochetes may be demonstrated sixteen to eighteen hours afterward.

Peripheral (tail) blood uniformly requires a longer period than heart's blood to produce an infection, and it may be possible that bodies antagonistic to the multiplication of the spirochetes are present in larger quantities in peripheral blood than in heart's blood.

Several rats were examined during periods of 14, 15 and 16 days after the paroxysm for the presence of spirochetes, but none were ever demonstrated, save in one case—Rat 37—when one atypical, straightened-out, swollen form was seen on the third day after the height of the infection.

When minimal amounts of infected peripheral blood were injected spirochetes would appear, usually after two or three days, in small numbers—viz.: one spirochete to from 13 to 500 fields. On the following day one spirochete to two fields might be counted, after which they would immediately disappear.

TABLE 3.—COURSE OF INFECTION IN RAT 22

Inoculated Dec. 4, 1907, a. m., from the tail blood of Mouse No. 17, when this blood contained one spirochete to 100 fields, about 15 drops of blood being used.

12/ 5—0 spirochetes in 300 fields	12/11—0 spirochetes in 300 fields
12/ 6—0 spirochetes in 300 fields	12/12—0 spirochetes in 300 fields
12/ 7—1 spirochete in 300 fields	12/13—0 spirochetes in 300 fields
12/ 8—1 spirochete in 2 fields	12/14—0 spirochetes in 300 fields
12/ 9—0 spirochetes in 300 fields	12/15—0 spirochetes in 300 fields
12/10—0 spirochetes in 300 fields	

The injection of larger quantities of heart's blood, or more severely infected blood from rats, was followed by the appearance of one spirochete to 25 or 100 fields within twenty-four hours, and after forty-eight hours from 25 to 100 spirochetes in 100 fields. At the end of seventy-two hours there was either complete disappearance or the presence of spirochetes in numbers of from 1 to 7 or more per field. On the fourth day, or at the end of ninety-six hours, it was extremely rare to find spirochetes in the peripheral blood. Rat 20 had one spirochete per 100 fields on the fourth day of the infection. Ordinarily the paroxysm lasted three days. (See Table 4, showing course of infection in Rat 20.)

The duration of the paroxysm and the number of spirochetes appearing in the peripheral blood of the inoculated rat do not depend entirely on the number of spirochetes injected, as the following experiment shows:

TABLE 4.—COURSE OF INFECTION IN RATS 19 AND 20

Inoculated 11/26/07 from heart's blood of Rat 18. Rat 18 had one spirochete to 500 fields when examined in the a. m. When examined six hours later, at time of death and subinoculation of Rats 19 and 20, there were two spirochetes to 100 fields in heart's blood.

Amount inoculated 0.3 c.c.	Amount inoculated, one-third as much as Rat No. 19, or 0.1 c.c.
11/27—1 spirochete to 50 fields	11/27—1 spirochete to 33 fields
11/28—1 spirochete to 25 fields	11/28—1 spirochete to 6 fields
11/29—2 spirochetes to 1 field	11/29—1 spirochete to 1 field
11/30—0 spirochetes to 300 fields	11/30—1 spirochete to 100 fields
12/ 1—0 spirochetes to 300 fields	12/ 1—0 spirochetes to 300 fields
Fourteen daily successive examinations were made without finding spirochetes.	Fourteen daily successive examinations were made without finding spirochetes.

In this experiment Rat 20, receiving at time of inoculation one-third as much infected blood as Rat 19, had a slightly severer infection and a longer paroxysm.

White rats may appear very slightly indisposed for half a day during the paroxysm. Only one death occurred; this was after the disappearance of spirochetes from the peripheral blood and was due to pneumonia.

White rats were infected directly from two different human sources, and in both instances the period of incubation was forty-eight hours, although large amounts of blood were used—2 c.c. and 5 c.c. of undiluted blood.

It is to be noted that during the course of the infection there are from thirty to fifty times as many spirochetes in rat's blood as in man's blood.

ANIMAL REACTIONS: WILD RATS

The gray rat (*Mus decumanus*), when kept in small cages for convenience in handling, does not survive captivity and the rather rough handling necessary in making inoculations. Most of the rats of this variety brought to the laboratory and confined in small cages died within a few days; consequently they were not suited for a study of this infection.

The black rat (*Mus rattus*) may be kept for weeks and months in small cages. Several black rats have been inoculated, and, as these rats were harboring *Trypanosoma lewisi*, an opportunity was offered for studying the parallel infection of trypanosomes and spirochetes.

Wild Rat 5 was inoculated intraperitoneally with one drop of blood from Mouse 5 and died on the third day. Spirochetes were not found at any time during the three days.

Wild Rat 25 was inoculated from Rat 24 when the latter had 8 spirochetes per 100 fields, using citrated heart's blood. This rat had a mild continuous in-

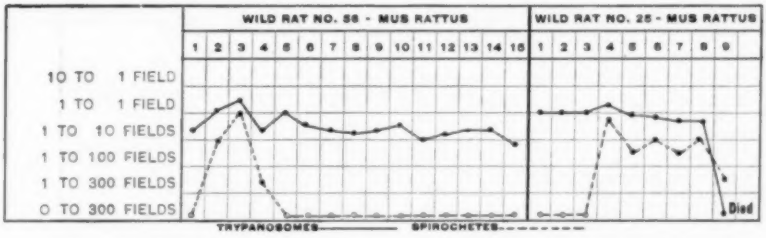

WILD RAT NO. 56 - MUS RATTUS
WILD RAT NO. 25 - MUS RATTUS
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
1 2 3 4 5 6 7 8 9
10 TO 1 FIELD
1 TO 1 FIELD
1 TO 10 FIELDS
1 TO 100 FIELDS
1 TO 300 FIELDS
0 TO 300 FIELDS
Died
TRYPANOSOMES
SPIROCHETES

Fig. 9.—Parallel infection of spirochete and trypanosomes.

fection lasting six days, after an incubation period of seventy-two hours. Death occurred at the end of the sixth day. This observation may have some importance on account of the possibility of a suctorial intermediary host conveying the spirochete from a rodent having a slight continuous infection to man.

Wild Rat 56 was inoculated from Rat 51 when the latter had 250 spirochetes to 100 fields, using citrated heart's blood injected subcutaneously at the base of the tail. This rat had an infection lasting three days after an incubation period of twenty-four hours.

ANIMAL REACTIONS: MONKEYS

The infection in monkeys of the old world, genus *Macacus*, is similar to that in man and white mice, inasmuch as there is more than one paroxysm.

Macacus 65 was inoculated on February 4 from Rat 63 when No. 63 had 219 spirochetes to 100 fields, using citrated heart's blood. One c.c. of blood was inoculated intraperitoneally. Spirochetes appeared after twenty-four hours and remained in the peripheral blood three days, disappearing for five days and then reappearing for three days in about the same numbers as in the first paroxysm. There was a slight diarrhea noticed after the second paroxysm. During each

paroxysm there was some bleeding from the gums near two carious, upper, middle incisors. This blood from the gums contained spirochetes. The animal did not appear sick at any time during the course of the disease.

The blood changes were slight polychromatophilia of red blood cells with some fine and coarse basophilic granular degeneration. These were noticed after the first paroxysm.

At the beginning of the second paroxysm there was a slight drop in the temperature followed by a rise of 4 degrees above normal to 106.4 F. The temperature was only slightly altered during the first paroxysm and was not greater than the variations noted during health. (See Fig. 10.)

ANIMAL REACTIONS: VARIOUS

A turtle, pigeon, frog and guinea-pig resisted an infection by infected rat's blood, which would have been sufficient to produce the disease in white rats. Two dogs and a goat were inoculated from human sources with blood obtained during paroxysms, but no infection resulted. It might have been possible to infect these animals if larger amounts of

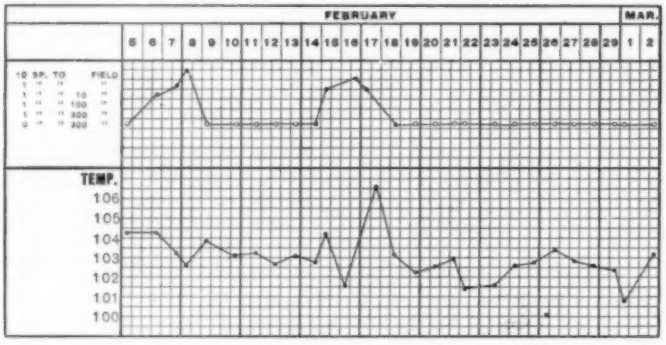


Fig. 10.—The spirochetal and temperature curve in Macacus 65. Note that there were only two paroxysms and that the temperature was not disturbed during the first one.

severely infected rat's blood could have been used, but the number of white rats at my disposal was so small that the greatest economy had to be exercised in subinoculations.

A raccoon has also resisted infection.

Novy and Knapp have shown that in the reactions of spirochetes and their hosts certain substances are produced which help to cause the disappearance of the spirochete from the blood and establish a qualified immunity against subsequent infections.

At the height of an infection it is evident that some change is taking place in the spirochete. Stretched out and irregularly curved forms are seen; many of these have achromatic zones. The movement of the

spirochete is less rapid, prefragmentation and chain formation are noticed and agglutination always occurs. Agglutinins and lysins are undoubtedly formed, but there is not a complete dissolution of the spirochete at this time. The sheath or periplast always appears to be intact in organisms seen in the blood stream. It is the internal substance of the spirochete that become fragmented (Fig. 11). Besides this, the spirochete apparently is not completely broken up in the peripheral blood stream, for fragments are never seen there, either free or in any type of leucocyte. If, however, as was observed by Levaditi and Manouélian,[23] with the spirochete of tick-fever, we sacrifice an animal at the height of an infection or a day or two later, it is possible, by Levaditi's silver impregnation methods, to demonstrate that the disappearance of the spirochetes from the blood stream has been due to the fact that

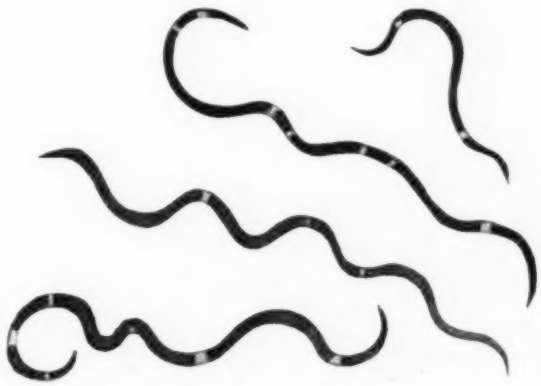


Fig. 11.—Spirochetes from blood of Rat 31 seen at height of infection, showing fragmentation of the protoplasmic substance, and an intact sheath or periplast.

they have been engulfed by endothelial cells lining the liver capillaries. Throughout the liver large, swollen endothelial cells may be seen, their cytoplasm dotted with spirochetes in all stages of fragmentation. From the appearance of the spirochetes within the endothelial cells it is probable that they are engulfed whole and that separation of the fragment occurs in the phagocytic cells by a solution of the periplasts.

23. Levaditi and Manouélian: Ann. de l'Inst. Pasteur, 1907, xxi, 295. Uhlenhuth and Haendel: Arb. a. d. k. Gsndhtsamte, 1907, xxvi, H. 1, 1. Manteufel Arb. a. d. k. Gsndhtsamte, xxvii, H. 2, 327. Schellack, C.: Arb. a. d. k. Gsndhtsamte xxvii, H. 2, 364.

The spirochetes disappear very rapidly from the peripheral blood after the height of the infection, but the disappearance is not complete, for on three occasions it has been possible to infect rats when no spirochetes could be demonstrated in films of the infective blood. In these instances the blood used was taken about twenty-four hours after the apparent disappearance of parasites from the peripheral circulation.

Fig. 12.—Endothelial cells from capillaries of the liver showing phagocyted spirochetes from Rat 26 killed at height of infection which had lasted three days. Levaditi pyridin preparation.

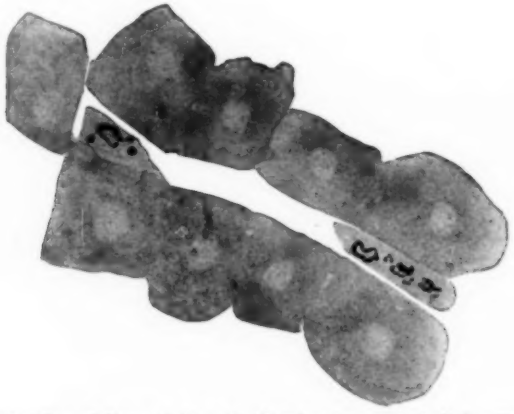


Fig. 13.—Section of liver of Rat 26, showing two endothelial cells of a capillary, containing phagocyted spirochetes. Levaditi pyridin preparation.

The following experiments illustrate this point:

Rat 57 was inoculated from Rat 55 when the latter had no spirochetes in 500 fields. Spirochetes appeared in the blood of No. 57 four days after inoculation.

Rat 57 was sacrificed when spirochetes had disappeared from the peripheral blood, which was injected into Rat 48, spirochetes appearing in the blood of Rat 48 on the sixth day, at the same time another rat, 49, was inoculated with an

emulsion of a portion of No. 47's liver in citrated saline solution; spirochetes appeared in No. 49's blood after an incubative period of four days, or two days less than in No. 48.

In this last experiment it is to be noted that the liver emulsion, although containing but traces of blood, the animal having been previously bled to furnish heart's blood for the inoculation of Rat 48, was more infectious than heart's blood from the same animal.

This experiment is interesting in view of the phagocytosis of spirochetes by liver endothelial cells. These experiments, besides showing the infectiousness of decline blood or of postdecline blood, show that phagocytosis plays an important part in the bodily defence.

If suitable emulsions containing liver endothelial cells can be prepared, it might be possible to demonstrate the production of specific opsonins during the infection.

IMMUNITY

During the course of the infection in white mice, white rats and wild rats a protective mechanism is developed which brings the infection to a close and confers a qualified immunity against a subsequent attack. The protective mechanism is one largely of phagocytosis, aided, as shown by Novy and Knapp, by specific agglutinins and lysins. The actively acquired immunity in white rats has lasted as long as forty-one days in individuals of the same strain. White mice have remained immune to the same strain sixty days; in fact, all attempts to reinfect animals with the same strain as that from which they were infected have failed, as the following experiments illustrate:

Active Immunity: Mice

Mouse 16 (inoculated December 20 from Mouse 14 with blood containing 1 spirochete to 38 fields) was formerly Mouse 3; spirochetes had been last seen in the blood November 7 or thirteen days previously. The immunity was sufficient to protect, spirochetes not being found in the blood during thirteen daily examinations.

Mouse 61 (inoculated January 28 from Rat 59 when No. 59 had 18 spirochetes to 10 fields, using citrated saline heart's blood intraperitoneally) was formerly Mouse 13, having had spirochetes in its blood for the last time on November 30. The immunity was complete, as No. 61's blood failed to show any spirochetes during subsequent daily examinations continued for nine days.

Active Immunity: Rats

Rat 43 (inoculated December 24 from Rat 38, when No. 38 had 420 spirochetes to 100 fields, using citrated heart's blood intraperitoneally followed by 10 drops saline solution of orcein) was formerly Rat 27, having had spirochetes in his blood for the last time December 16. The immunity was complete, spirochetes failing to appear in No. 43's blood during the nine days subsequent to the last inoculation.

Rat 58 (inoculated January 25 from Rat 57 which had 3 spirochetes to 100 fields, using citrated saline heart's blood intraperitoneally) was formerly Rat 45.

having had spirochetes in his blood from December 29 to 31 inclusive. The immunity was complete, spirochetes failing to appear during thirteen days.

Rat 69 (inoculated January 28 from Rat 59 when No. 59 had 18 spirochetes to 10 fields, using citrated heart's blood intraperitoneally) was formerly Rat 33, having had spirochetes in his blood from December 16 to 18 inclusive. The immunity was complete, spirochetes failing to appear during ten days.

SPECIFIC CHARACTER OF STRAINS

The immunity conferred by one strain of spirochetes is not sufficient to protect against a second strain of the same species having a different origin. For example, I found that, while it was impossible to reinfect white mice or white rats with strain A, the one used to infect them originally, it was possible to infect them by using strain B. The history of these two strains has been given above. Strain A was obtained from Case 3 Oct. 11, 1907, during the antepenultimate paroxysm, passed through 16 white mice and about 50 white rats. Strain B was obtained more recently from a case occurring in Colon Hospital. Blood was drawn during the penultimate paroxysm and has been passed through 8 rats and one mouse. The chief differences between the strains consist in the fact that B was more recently obtained from its human host and that it has had a shorter residence in animals. Clinically the patients supplying these two strains had the isthmian type of fever. Morphologically there are no differences between the two strains of spirochetes. Parallel inoculations of strains A and B into animals immunized to A have been made, with the result that animals which had recovered from an infection by A could be infected by B, yet would be immune to A. The period of incubation was sometimes prolonged and the number of spirochetes few; yet, on the other hand, the infection by B in two animals immunized to A was prompt and severe, and in one—Rat 67—the infection by A in an animal immunized to B was also prompt and severe.

In this experiment a rat infected by and presumably immune to strain B was promptly infected by strain A nine days after the disappearance of strain B. This proves that the difference in the activity of the strains is not one of relative virulence, but is due to there being specific strains with specific immunizing powers. This is the most important fact developed in the course of the investigation and is of the greatest value in connection with any attempts to derive a curative or preventive serum; it is suggestive in explanation of the fact mentioned by Vandyke Carter and others that one attack of relapsing fever does not confer a high degree of immunity, for an individual becoming infected by one strain in a given locality might well be non-immune with regard to other strains in that locality.

TABLE 5.—IMMUNITY AND INFECTION IN MICE 17 AND 13

Mouse 17, inoculated Nov. 23, '07 from Mouse 13, when No. 13 had 1 spirochete to 10 fields. Immediately after the inoculation 5 c.c. blood was drawn from Rats 1 and 7, which had an infection, and injected subcutaneously into Mouse 17. (Passive Immunity Experiment.)

11/24	No	spirochetes in	300 fields
11/25	No	spirochetes in	300 fields
11/26	No	spirochetes in	300 fields
11/27	1	spirochete in	5 fields
11/28	1	spirochete in	1 field
11/29	No	spirochetes in	300 fields
11/30	No	spirochetes in	300 fields
12/ 1	No	spirochetes in	300 fields
12/ 2	No	spirochetes in	300 fields
12/ 3	No	spirochetes in	300 fields
12/ 4	1	spirochete in	100 fields
12/ 5	1	spirochete in	300 fields
12/ 6	1	spirochete in	100 fields
12/ 7	No	spirochetes in	300 fields
12/ 8	No	spirochetes in	300 fields
12/ 9	No	spirochetes in	300 fields
12/10	No	spirochetes in	300 fields
12/11	1	spirochete in	69 fields
12/12	1	spirochete in	20 fields
12/13	8	spirochetes in	100 fields
12/14	No	spirochetes in	300 fields
12/15	No	spirochetes in	300 fields
12/16	No	spirochetes in	300 fields
12/17	No	spirochetes in	300 fields
12/18	No	spirochetes in	300 fields
12/19	No	spirochetes in	300 fields
12/20	No	spirochetes in	300 fields
12/21	No	spirochetes in	300 fields

Mouse 13, inoculated Nov. 12 from Mouse No. 12 when No. 12 had fewer spirochetes than 1 to 500 fields.

11/13	No	spirochetes in	300 fields
11/14	No	spirochetes in	300 fields
11/15	No	spirochetes in	300 fields
11/16	No	spirochetes in	300 fields
11/17	1	spirochete in	14 fields
11/18	1	spirochete in	75 fields
11/19	No	spirochetes in	300 fields
11/20	No	spirochetes in	300 fields
11/21	Not examined.		
11/22	No	spirochetes in	300 fields
11/23	1	spirochete in	10 fields
11/24	No	spirochetes in	300 fields
11/25	No	spirochetes in	300 fields
11/26	No	spirochetes in	300 fields
11/27	No	spirochetes in	300 fields
11/28	No	spirochetes in	300 fields
11/29	No	spirochetes in	300 fields
11/30	1	spirochete in	300 fields
12/ 1	No	spirochetes in	300 fields
12/ 2	No	spirochetes in	300 fields
12/ 3	No	spirochetes in	300 fields
12/ 4	No	spirochetes in	300 fields
12/ 5	No	spirochetes in	300 fields

TABLE 6.—INFECTION AND IMMUNITY IN MICE B-8 (17) AND 61 (13)

January 28, Mouse 17 (which became Mouse B-8) inoculated from B-5 when B-5 had 14 spirochetes to 100 fields, using citrated heart's blood intraperitoneally.

1/29	No	spirochetes in	300 fields
1/30	No	spirochetes in	300 fields
1/31	No	spirochetes in	300 fields
2/ 1	4	spirochetes in	100 fields
2/ 2	7	spirochetes in	100 fields
2/ 3	2	spirochetes in	100 fields
2/ 4	No	spirochetes in	300 fields
2/ 5	No	spirochetes in	300 fields
2/ 6	No	spirochetes in	300 fields
2/ 7	1	spirochete in	200 fields
	Sacrificed		

In this experiment the mouse, while having an actively acquired immunity to Strain A, was infected by Strain B. Controlled by Mouse 61 (13).

January 28, Mouse 13 (which became Mouse 61) inoculated with citrated blood from the heart of No. 59 when 59 had 18 spirochetes to 10 fields.

1/29	No	spirochetes in	200 fields
1/30	No	spirochetes in	200 fields
1/31	No	spirochetes in	200 fields
2/ 1	No	spirochetes in	200 fields
2/ 2	No	spirochetes in	400 fields
2/ 3	No	spirochetes in	200 fields
2/ 4	No	spirochetes in	200 fields
2/ 5	Not examined.		
2/ 6	No	spirochetes in	200 fields

In this experiment the mouse having an actively acquired immunity to Strain A was still immune after 59 days to Strain A. Control to Mouse B-8 (17).

Rats 36 and 37, immunized to strain A, having had spirochetes in their blood on December 21 for the last time, were inoculated on January 24 by strain B. The animals inoculated by strain B showed a prompt and severe infection.

TABLE 7.—COURSE OF INFECTION IN RATS 36 AND 37

Rat 36, inoculated December 18, p. m. from Rat 30 when No. 30 had 148 spirochetes to 100 fields, using citrated heart's blood intraperitoneally.

12/19	13	spirochetes to	100 fields
12/20	220	spirochetes to	100 fields
12/21	360	spirochetes to	100 fields
12/22	No	spirochetes to	300 fields
12/23	No	spirochetes to	300 fields
12/24	No	spirochetes to	300 fields
12/25	No	spirochetes to	300 fields
12/26	No	spirochetes to	300 fields
12/27	No	spirochetes to	300 fields

Rat 37, inoculated December 18, p. m., from Rat 30 when No. 30 had 148 spirochetes to 100 fields, using citrated heart's blood intraperitoneally.

12/19	8	spirochetes to	100 fields
12/20	140	spirochetes to	100 fields
12/21	120	spirochetes to	100 fields
12/22	No	spirochetes in	300 fields
12/23	No	spirochetes in	300 fields
12/24	1 atypical spirochete in		300 fields
12/25	No	spirochetes in	300 fields
12/26	No	spirochetes in	300 fields
12/27	No	spirochetes in	300 fields

TABLE 8.—COURSE OF INFECTION IN RATS B-3 (36) AND B-4 (37)

January 24, Rat 36 (which became Rat B-3), inoculated with Strain B from Rat B-1 when B-1 had 8 spirochetes to 1 field, using citrated heart's blood intraperitoneally.

1/25—18 spirochetes to 10 fields

January 24, Rat 37 (which became Rat B-4) inoculated from Rat B-1 when B-1 had 8 spirochetes to 1 field, using citrated heart's blood intraperitoneally.

1/25—43 spirochetes to 10 fields
1/26—10 spirochetes to 1 field
1/27—No spirochetes to 300 fields
1/28—No spirochetes to 300 fields; died.

Furthermore a rat (B-2) immunized to strain B was inoculated eight days after the disappearance of spirochetes from his peripheral blood, with spirochetes from Rat 53, strain A. The rat became infected within twenty-four hours and experienced a moderately severe infection.

TABLE 9.—COURSE OF INFECTION IN RAT B-2

Rat B-2, inoculated Jan. 24 from No. B-1 when the latter had 8 spirochetes to 1 field, using citrated saline heart's blood intraperitoneally.

1/25— 2 spirochetes to 1 field
1/26—20 spirochetes to 1 field
1/27—No spirochetes to 300 fields
1/28—No spirochetes to 300 fields
1/29—No spirochetes to 300 fields
1/30—No spirochetes to 300 fields
1/31—No spirochetes to 300 fields
2/ 1—No spirochetes to 300 fields
2/ 2—No spirochetes to 300 fields
2/ 3—No spirochetes to 300 fields
2/ 4—No spirochetes to 300 fields

TABLE 10.—COURSE OF INFECTION IN RAT 67 (B-2)

2/4—Inoculated Rat B-2 (which became Rat 67) from Rat 63, Strain A, when the latter had 210 spirochetes per 100 fields, using citrated neck blood intraperitoneally.

2/5— 25 spirochetes to 100 fields
2/6—340 spirochetes to 100 fields
2/7— 32 spirochetes to 100 fields

PASSIVE IMMUNITY

Two attempts have been made to produce passive immunity by the subcutaneous injection of blood from a convalescent animal a moment after infected blood had been injected intraperitoneally.

Mouse 17, inoculated December 23 from Mouse 13, when the latter had one spirochete in 10 fields. Immediately afterward blood was drawn from the tail of Rat 7, formerly No. 1, 0.5 c.c. of blood being used and injected subcutaneously. Rat 7, formerly No. 1, had been infected with human blood strain A October 11, and was subsequently inoculated with blood from infected Mouse 2. This quantity of blood from an animal which had recovered was not sufficient to prevent a severe infection in Mouse 17 with three paroxysms after an incubation period of four days.

Rat 45, inoculated December 27, from Rat 41, when the latter had 450 spirochetes to 100 fields; inoculation intraperitoneal followed by a subcutaneous injection of 5 drops of heart's blood from Rat 31, whose blood had been free from spirochetes for nine days. This quantity of blood from a convalescent was not sufficient to prevent Rat 45 becoming infected after a period of forty-eight hours.

Blood from convalescents, therefore, in the quantities used is of no value in preventing an infection. The period of incubation, however, as in Rat 45 and Mouse 17, may be prolonged.

In these experiments very large amounts of infected blood were not used in the attempts to infect or reinfect animals. Only that quantity was used which was amply sufficient to cause the disease in a susceptible

non-immune animal. When very large quantities of blood are used the contained spirochetes become disseminated through the blood stream of the inoculated animal; they are merely diluted and their presence does not positively mean that they have multiplied within the blood stream.

HYPERIMMUNITY: PREVENTION

A goat has been gradually hyperimmunized, in addition to its natural immunity, by successive injections of infected white rat's blood, containing strains A and B, and one injection of blood from human source (Case 1). In all, 11 subcutaneous injections of infected blood have been given from three human sources.

TABLE 11.—INOCULATIONS RECEIVED BY GOAT

Inoculation Blood From—	Inoculation Blood From—
7/31, 1907—Lindoff, Case 1	1/ 2, 1908—Rat 46, Strain A
12/ 6, 1907—Rat 21, Strain A	1/11, 1908—Rat 49, Strain A
12/12, 1907—Rat 24, Strain A	1/16, 1908—Rat 51, Strain A
12/15, 1907—Rat 26, Strain A	1/24, 1908—Rat B-1, Strain B
12/24, 1907—Rat 38, Strain A	1/28, 1908—Rat 59, Strain A
12/27, 1907—Rat 41, Strain A	

Serum was collected from this goat February 6, 5 p. m., placed in a refrigerator at 51 degrees F. until the following afternoon, when it was used in the two following experiments:

Mouse 68, inoculated February 7, 3 p. m., from Rat 66, which had 90 spirochetes to 100 fields, using citrated peripheral tail-blood, 2 drops intraperitoneally, followed immediately by an intraperitoneal injection of 5 c.c. of hyperimmune goat serum. Spirochetes appeared in Mouse 68 on February 13, 2 spirochetes to 100 fields, or after the prolonged incubation period of six days. Most of the mouse's red blood corpuscles were diminished in size, strongly resembling goat's red blood corpuscles; the larger red blood corpuscles showed considerable polychromatophilia and fine granulations, but no basophilic granulation was noticed.

TABLE 12.—COURSE OF INFECTION IN MOUSE NO. 68

Date of Inoculation. 1908	Notes.
February 7, 3 p. m.	
February 8.	
February 9.	
February 10	—No spirochetes in 400 fields; most of the red blood corpuscles are small—goat size, and the larger ones show polychromatophilia and granular degeneration—no basophilia.
February 11	—No spirochetes in 300 fields. Red blood corpuscles same as on the 10th.
February 12	—No spirochetes in 300 fields. Polychromatophilia increased; 60 per cent. of the r. b. c. are polychromatophilic. R. b. c. increasing in size.
February 13	— 2 spirochetes to 100 fields.
February 14	—24 spirochetes to 100 fields.
February 15	—No spirochetes to 300 fields.
February 16	—No spirochetes to 300 fields. Polychromatophilia still marked. R. b. c. normal size.
February 17	— 2 spirochetes to 100 fields.
February 18	—16 spirochetes to 100 fields.
February 19	—12 spirochetes to 100 fields. Polychromatophilia diminishing. R. b. c. normal size. Died. Spleen enlarged. Autopsy otherwise negative.

TABLE 13.—COURSE OF INFECTION IN MOUSE 69

Date of Inoculation. 1908	Notes.
February 7	(3 p. m.)—From Rat No. 66, when the latter had 90 spirochetes to 100 fields, using 2 drops of citrated tail-blood, followed by a subcutaneous injection 0.7 c.c. hyperimmune goat-serum.
February 8.	
February 9	—No spirochetes in 300 fields.
February 10	—No spirochetes in 300 fields. Blood shows many small goat-size r. b. c. The larger normal size corpuscles are polychromatophilic and finely granular.
February 11	—No spirochetes in 300 fields.
February 12	—No spirochetes in 300 fields.
February 13	—20 spirochetes in 100 fields.
February 14	—No spirochetes in 400 fields.
February 15	—No spirochetes in 300 fields.
February 16	—No spirochetes in 300 fields. Polychromatophilia still marked. R. b. c. normal size.
February 17	— 3 spirochetes to 100 fields.
February 18	—12 spirochetes to 100 fields.
February 19	— 1 spirochete to 300 fields.
February 20	—No spirochetes to 300 fields. Polychromatophilia much diminished. R. b. c. normal size.
February 21	— 1 spirochete to 300 fields.
February 22	—No spirochetes to 300 fields—and none in 5 successive daily examinations.

In this experiment the period of incubation was greatly and equally prolonged in both mice, although Mouse 68 received about seven times as much serum as Mouse 69, and this intraperitoneally. Mouse 68 died during the second paroxysm, while Mouse 69 had a light primary paroxysm and a very mild secondary paroxysm. There was considerable blood destruction in each mouse. The supply of rats became exhausted at this time, so that it was not possible to increase the immunizing substances in the goat serum. A serum of this strength and character, in the quantity used, apparently merely prolongs the period of incubation, for, after the injection of the hyperimmune serum, the immunizing substances are very possibly slowly eliminated or rendered inert; the spirochetes then multiply as in an animal receiving a minimum amount of infected blood without the addition of immune serum.

It was necessary to use white mice in this experiment so as to avoid excessive hemolysis, the goat having been immunized with infected white rat's blood, which had rendered the goat serum hemolytic for the red blood corpuscles of the white rat.

HEREDITARY IMMUNITY

No opportunity arose for making observations on the immunity resulting from infection through the placenta.

PREVENTION BY VACCINATION

The results of experiments on the immunization of rats and mice with strains A and B show conclusively that curative or preventive serums, if derived at all, must be obtained by the inoculation of several strains. Polyvalent serums must be used and the question arises as to

whether it will be necessary to hyperimmunize an animal to each of the strains or whether, perhaps, single inoculations of a large number of strains may be sufficient to hyperimmunize.

A method of treatment not yet investigated is that of vaccination. This is suggested on account of the fact that phagocytosis plays an important part in the protective mechanism against the infection. In the investigation of this question it will be necessary to devise a practicable method for the cultivation of the spirochetes.

INFLUENCE ON THE INFECTION OF DRUGS ADMINISTERED HYPODERMICALLY

A few experiments were carried out to determine the influence, if any, of certain aniline dyes and other substances on the course of the disease in rats. The following substances were used:

Neutral red.
Congo red.
Orcein.
Saffranin.
Bordeaux red.
Sulphanilic acid.
Quinin and urea hydrochlorate.
Methylene blue.

Saturated solutions of these substances in normal saline solution were injected subcutaneously immediately after a peritoneal injection of infected blood had been given. A control rat was always inoculated at the same time. The result of such injection in almost every instance was an earlier and more severe infection than in the control rat which had not been treated with the dyes.

Methylene blue, when given in very large doses, prevented an infection, but the animals were profoundly poisoned by the drug and died on the second and third day. Dilute solutions of methylene blue were of no value in preventing an infection. The minimal protective dose of methylene blue could not be worked out at this time, but the use of methylene blue and allied substances seems to afford a favorable line for investigation.

In two experiments with orcein such heavy infections followed that it was thought that orcein might break down an actively acquired immunity; accordingly Rat 27, having passed through an infection between December 13 and 15, was inoculated from infected Rat 38 and treated hypodermically with 10 drops of saturated solution of orcein in normal saline solution; the animal failed to become infected. Orcein,

therefore, in the quantity used can not destroy an actively acquired immunity.

PARALLEL INFECTION WITH SPIROCHETES AND TRYPANOSOMA LEWISI, IN MUS RATTUS

There is no striking modification of a trypanosomal infection in rats by the parallel infection with spirochetes, nor, on the other hand, are the spirochetes affected by the presence of trypanosomes. In one instance (Rat 56) the trypanosomes increased at equal pace with the spirochetes, but the trypanosomes remained in the blood continuously for weeks after the spirochetes had disappeared. (See Fig. 9, chart of parallel infection of trypanosomes and spirochetes.)

TRANSMISSION OF RELAPSING FEVER

The transmission of African relapsing fever by means of infected ticks, *Ornithodoros moubata,* from monkey to monkey was accomplished by the late T. Everett Dutton and John S. Todd of the Liverpool School of Tropical Medicine in 1904. During the next year infected ticks were sent to Liverpool, and from these ticks monkeys were infected. Dutton and Todd were also successful in transmitting the spirochetes by the bites of young ticks newly hatched in the laboratory from eggs laid by infected parents.

Breinl, Kinghorn and Todd were unsuccessful in their attempts to transmit *Sp. duttoni* or *Sp. obermeieri* from monkey to monkey by means of bedbugs. The analogous disease in fowls, as determined by Marchoux and Salimbeni,[24] is transmitted by a tick, *Argus miniatus.*

In an interesting note concerning the earliest mentioned epidemics in Great Britain Begbie quotes Welsh, who wrote from Edinburgh in 1819, as follows:

> When acting as a clerk in the Royal Infirmary, in the course of four months my three colleagues, two of the young men in the apothecary shop, two housemaids and thirteen or fourteen nurses caught the disease and the matron and one of the dressers died of it. Since I left the Infirmary three more of the gentlemen acting as clerks, one of the young men in the shop and many more of the nurses have caught the infection. When it begins in a family we always expect more than one of them to be affected. I could mention instances of 4, 5, 6 and 7 being sent to the hospital out of one family; 8, 9 and 10 out of one room; 20 and 30 out of one stair and 30 and 40 out of one close, and this all in the course of a few months. Hardly any of the nurses, laundry-women or others coming in contact, either with the patients or their clothes, have escaped. At one time there were 18 nurses off duty from the fever. It appears sufficiently remarkable that, as specially noted by Dr. Connant in 1843 and 1844, laundry-women engaged in washing the clothes of the sick, though never brought into direct communication with the patients themselves, suffered frequently from the disease.

24. Marchoux, E., and Salimbeni, A.: Am. de l'Inst. Pasteur, 1903, xvii, 569.

After reading the accounts of epidemics of relapsing fever, together with our knowledge of the mode of transmission of tick fever and spirillosis in fowl and Mackie's observations in India, one can hardly escape the belief that the spirochetes of our local relapsing fever are conveyed mechanically or by an intermediary host in the person of some suctorial insect or acarid—fleas, bedbugs, ticks, lice or mosquitoes. The disappearance of relapsing fever for long periods after extensive epidemics from some localities, such as Scotland and Ireland; the failure of the disease to assume any extensive character in the United States and certain other places after introduction, and the limitation of the disease frequently to recently arrived immigrants or sailors and to seaport or neighboring towns, point strongly to a suctorial insect as the agent of transmission, and render it highly probable that the conditions for the existence of this host are not favorable in the United States and certain other places, either due to the fact that the suctorial host does not survive, or that it does not possess a suitable alternate host to subsist on when man is not available.

There is no evidence to prove the necessity of contact as in syphilis or in dourine or *mal de coit*, the trypanosomal disease of horses transmitted during copulation. Inoculation is accomplished with ease, for in two laboratories where animal inoculations have been made with *Sp. duttoni* and *Sp. obermeieri* two investigators and three assistants have been infected through an abraded skin during an autopsy on a severely infected monkey and by the bites of infected monkeys. Recently Mackie, of Bombay, has made an important contribution to our knowledge of the transmission of *Sp. carteri* by *Pediculus corporis*. Mackie studied an outbreak of Bombay relapsing fever at the Nasik Mission Settlement. He found that 14 per cent. of lice taken from the heavily infected boys' ward, 2 per cent. taken from the scantily infected girls' ward and 13 per cent. of artificially fed lice showed multiplication of spirilla in internal organs.

Attempts have been made at the laboratory here to infect animals by means of ticks, but all efforts have been unsuccessful. At the suggestion of Mr. C. L. Marlatt, of the Department of Agriculture, several specimens of *Amblyomma*[25] were tried with rats. These ticks, *Amblyomma dissimile*, taken from iguanas, and *Amblyomma cajennense*, taken from dogs, have long biting parts and are dislodged from their cus-

25. During excursions out into the bush and jungle, I find that specimens of *Amblyomma* (species undetermined) larval and adults, readily attach themselves and feed voraciously.

tomary host with difficulty, but they are probably too large to be used in the transmission experiments with rats.

The ecto-parasites of rats are generally quite small, fleas, mites and small ticks. The common dog tick of Panama, *Rhipicephalus texanus*, has shorter biting parts and is more easily dislodged. This tick will attach itself to rats, but unless the rat is immobilized the ticks are rapidly killed and eaten.

CONCLUSIONS

The relapsing fever of Panama is distinct from the analogous fever of Africa, Europe and Asia, although belonging to the same general class.

The micro-organism causing the local relapsing fever belongs to the group containing *Sp. obermeieri, Sp. duttoni* and *Sp carteri.*

This spirochete causes a recurring infection in man, monkeys (genus *Macacus*) and white mice, and single paroxysms in white and wild rats.

The animal reactions are similar to those obtained by Norris, Pappenheimer, Fleurnoy, Novy and Knapp, with the organism erroneously identified by the latter two as *Spirillum obermeieri.*

The blood of animals very recently recovered from an infection and that between paroxysms, where spirochetes are apparently absent from the peripheral blood, is infectious, and by analogy this affords a valuable means of diagnosis of the fever in man during the afebrile period by the inoculation of susceptible animals, mice and rats with patient's blood.

There is considerable variation in the morphology of the spirochete in the same strain and sometimes in the same smear.

Identification of spirochetes can not be made with certainty on morphologic grounds.

The mechanism of defense is largely that of phagocytosis by hepatic endothelium.

Infected animals sacrificed at different stages of the infection show, as the disease advances, an increasing number of fragmented spirochetes, engulfed by endothelial cells of the liver.

In animals which had recently recovered from an infection a liver emulsion is more infectious than heart's blood. This suggests the probable vitality and unity of fragments.

Infection by one strain of spirochetes is followed by a considerable degree of active immunity for that strain, but such immunity is not potent against another strain from a different source, although of the same species and from the same locality but from a different human host.

For the production of preventive and curative serums polyvalent sera derived from all the strains will probably be necessary.

The blood, in moderate amounts, of subjects which have recovered, is of no value in preventing infections in white mice and white rats.

Relapses may be explained by the multiplication of spirochetes in out-of-the-way places where they do not enter the portal circulation and can not be engulfed by liver endothelium.

Agglutination of spirochetes occurs at least twenty-four hours before the crisis in rats *in vitro* and *in vivo*.

This spirochete is probably a spiral ribbon and not a spiral cylinder.

The group of spiral-shaped micro-organisms needs reclassification on a basis of morphology, pathogenity and habitat.

This spirochete is more closely related to bacteria than to protozoa.

The rôle of the spleen is similar to that observed in anemia.

With suitable emulsions of liver substance and immune serums it should be possible to demonstrate specific opsonins.

The natural mode of infection is probably by means of an intermediary host—some suctorial insect or acarid, either directly or by means of an alternate host, such as a wild rat or other susceptible animal.

I wish to express my indebtedness to the following gentlemen for various courtesies:

To Drs. Sommersgill and Brem for calling my attention to cases favorable for animal inoculations and for clinical data; to Major Ronald Ross, Dr. A. Breinl and Dr. S. J. Goldfarb for temperature charts, and to Col. W. C. Gorgas and Lieut.-Col. J. L. Phillips for permission to publish.

REPORT OF A CASE OF STOKES-ADAMS' DISEASE*

THEODORE B. BARRINGER, JR., M.D.
NEW YORK

This case presents several interesting features, similar instances of which have not as yet been reported.

Patient.—A blacksmith was admitted to the wards of the fourth medical division of Bellevue Hospital, suffering from acute gout, involving the knee and large toe joints. He had had several previous attacks of gout and twenty years earlier a chancre with well-marked secondary symptoms. He had used alcohol to excess for years. He also complained of attacks of vertigo and syncope.

Physical Examination.—An obese man, five feet seven inches tall, somewhat dyspneic. The apex beat is in the fifth left interspace, four and one-half inches from the median line, and distinctly heaving. The outlines of the heart are difficult to determine on account of the thick chest wall. The heart action is slow and regular, 44 to the minute, and the sounds are normal except for an accentuated aortic second. At the aortic area a systolic murmur is heard transmitted upward. There are no sounds heard during the diastolic pause. The radial pulse is 44 to the minute and of increased tension (the systolic pressure varied between 160 and 170). The radials and brachials are sclerosed. The edge of the right lobe of the liver is felt three inches below the ribs in the mammary line.

The tracings shown in Figures 1 and 2 were taken from the apex-beat, liver and radial artery. It will be seen that the auricular rhythm bears no constant relation to the ventricular rhythm; that is, the patient is suffering from complete auriculoventricular dissociation. At the time these particular records were taken, the auricular rate was 69 and the ventricular rate 39 per minute.

The marked auricular liver pulse is unusual in cases of heart-block and is probably a coincidence, having nothing to do with the essential heart lesion. Its significance is doubtful. Mackenzie believes it to be due, in a majority of cases, to tricuspid stenosis.

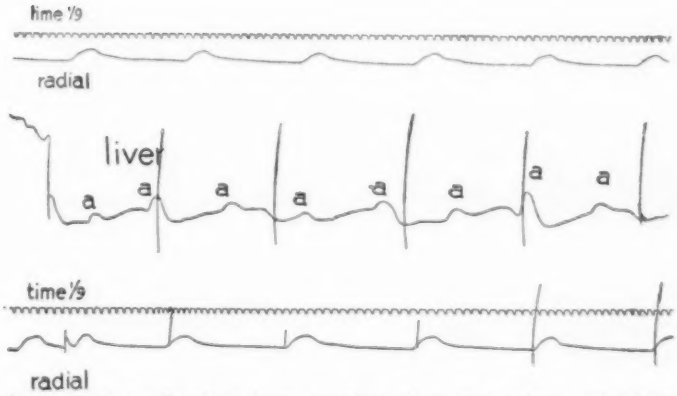
The patient remained under treatment for several months. During this time he had three attacks of vertigo and two syncopal attacks, once falling and cutting his forehead. Unfortunately, he was not seen until some minutes after each of these attacks, so I could not tell if they were preceded by a slowing of the ventricles.

The condition of complete dissociation continued for a week after admission and then gradually disappeared, the pulse increasing through several days until it reached 68 to 80 per minute. After a few days of normal rate the block again returned gradually and persisted a few days. His longest period of blocking was ten days, and his longest period of normal rate was three weeks. On several occasions, as was to be expected, the tracings showed a partial block with two-to-one rhythm. During his normal period the auriculoventricular interval was not lengthened, and the auricular liver pulse persisted.

---

*From the Department of Medicine of Cornell University Medical College.

Atropin has been used by a number of observers in cases of heart-block to test the degree of dissociation. Its usually observed mode of action is as follows: In complete block the auricular rate is markedly increased, while the ventricular rate is practically uninfluenced. In partial block, where some of the auricular impulses pass over to the ventricle, atropin increases the auricular rate, and therefore the number of transmitted auricular stimuli, and so the ventricular rate. The usual explanation of this action of atropin is that it paralyzes the terminal cardiac filaments of the vagus nerve, which presumably exist only in the auricles. So atropin, or any measure acting on the vagus nerve, can in-



Figs. 1 and 2.—Tracings from apex-beat, liver and artery. The letter *a* represents waves due to the contraction of the left auricle in the apex tracing, and the right auricle in the liver tracing.

fluence the ventricle only indirectly, provided, of course, that the auriculoventricular bundle is capable of transmitting the impulse.

Tabora[1] has shown, however, in the course of some experiments with the action of digitalis on dogs, that the vagus nerve has a markedly elective influence on the conductivity of the auriculoventricular bundle. If this view is correct, a case such as ours, with an auriculoventricular

1. Tabora: Ztschr. f. exper. Path. u. Therap., 1906 iii, 549.

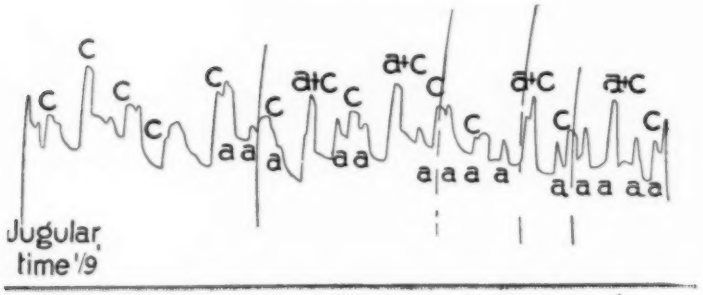


Fig. 3.—Tracing showing auriculoventricular dissociation.

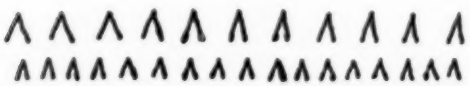


Fig. 4.—Diagram from Figure 3; upper lines, reconstructed *c* waves; lower lines, reconstructed *a* waves.

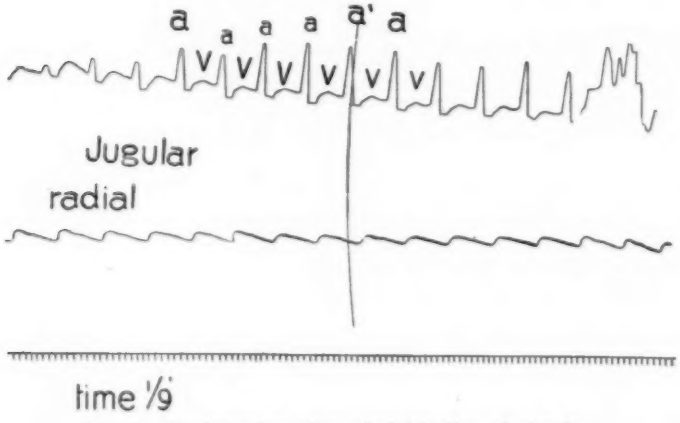


Fig. 5.—Tracing taken after administration of atropin.

bundle showing marked variations in its conductivity, ought to be very favorably influenced by atropin, which would remove this inhibitory vagus effect. This experiment was accordingly carried out.

The tracing shown in Figure 3 was taken at 2:10 p. m. For five days previous, a condition of partial or complete block had existed, the pulse varying between 40 and 50 per minute. This shows a complete dissociation, with a ventricular rate of 39 and an auricular rate of 59 per minute. The absence of relation between auricular and ventricular systoles is recognized more easily in the diagram (Figure 4) constructed from the tracing.

At 2:12, 1/50 grain of atropin was given by hypodermic injection. At 2:27 the pulse rate had increased to 61, and at 2:47 the tracing shown in Figure 5 was taken.

This shows an absence of block with auricular and ventricular rate of 74 to the minute. That evening the radial pulse was 44 per minute, and for the next thirty-six hours from 44 to 48 per minute.

This experiment supports the view that the vagus nerve influences the conductivity of the auriculoventricular bundle. It shows, moreover, that atropin can not always be depended on to determine whether a block is complete or not. Tabora[1] also demonstrated in his experimental work that vagus action alone can not produce dissociation: an additional factor is necessary, either anatomical change in the auriculoventricular bundle or a damaging of its conductivity.

Consideration of this experimental work, together with the age of our patient, his arteriosclerosis, and the history of syphilis, make it probable that there was some morphological change in the auriculoventricular bundle. The inhibitory action of the vagus on the damaged bundle decreased its conductivity so much further that the varying degrees of dissociation were produced.

I am indebted to Dr. Alexander Lambert for the privilege of reporting this case.

34 West Eighty-fourth Street.

BOOK REVIEW

A Treatise on Diagnostic Methods of Examination. By Prof. Dr. H. Sahli, of Bern. Edited, with additions, by Francis P. Kinnicutt, M.D., Professor of Clinical Medicine, Columbia University, New York; and Nath'l Bowditch Potter, M.D., Visiting Physician to the City Hospital and to the French Hospital, and Consulting Physician to the Manhattan State Hospital, New York. Philadelphia and London: W. B. Saunders & Co., 1905. Octavo of 1008 pages, profusely illustrated. Cloth, $6.50 net; half morocco, $8.00 net.

The early appearance of a second American edition of Sahli's Diagnostic Methods is evidence of the usefulness and popularity of this excellent work, the special strength of which lies probably in the fact that, as pointed out by the author in the preface, it is not a mere compilation. One may indeed turn to most of the sections and find a good discussion of diagnostic methods by a wise and experienced observer. It is a well-rounded work in which the personal experience of the author is evident at many points.

Nothing could be sounder than the remarks on percussion (page 154) and the statement that " . . . the percussion note which is loud enough to be heard at considerable distance is generally faulty." The observation on page 265 apropos of auscultation of the heart that "we should always auscultate the patient in different positions, particularly standing and lying down," is too often forgotten.

A large section (pp. 397 *et seq.*) is devoted to a detailed description of the Sahli-Seiler butyrometric method of examination of the gastric functions. The terminal section on diseases of the nervous system is extensive and useful.

The book is so well known that an extended review is not necessary.

Professor Sahli has been happy in the editors of the American edition. The translation is good, the remarks which have been added by the American editors are often helpful and many of the new illustrations are excellent and real additions to the work.

A few minor notes of suggestion or criticism may not, however, be out of place.

It is a pity that a more thorough description of the venous pulse should not have been included in the section on examination of the heart and vessels, and again, although in the supplement some of Wenckebach's work has been reviewed, one misses the judicious summary of modern researches so valuable in other parts of the work.

The description of the cardiogram (p. 298) is not what might be desired. It is also rather surprising (pp. 177-8) that so good an observer as the author should fail to recognize the ease with which the right heart may be outlined by careful percussion in most cases. Indeed, the diagrams on these two pages are not wholly in conformity one with another.

The illustration introduced by the American editors on page 181 is hardly happy. In the experience of the reviewer percussion has never given so obtuse a cardio-hepatic angle excepting in pericardial effusions.

M. Huchard would probably be somewhat surprised to find himself referred to on p. 260 as "von Huchard."

It would be well if the terminology of animal parasites should be brought into concordance with the now recognized rules of zoölogical nomenclature. There would seem to be small reason to-day for the doubt expressed on p. 435 as to the pathological significance of *Strongyloides stercoralis,* which is here called incorrectly *Anguillula intestinalis* and *stercoralis.* Again, it would have been well for the American editors to point out the rarity of *Tænia solium* in the United States.

In the section on examination of the blood no mention is made of the very valuable modifications of Romanovsky's stain, such as Leishman's, Wright's and Hastings'.

The reviewer can not agree with the author in his advice that the term "Hodgkin's disease" be dropped. The observations of Dorothy Reed would seem to justify the classification of this variety of disease of the lymphatic apparatus as an entity either as Hodgkin's disease or lymphadenoma.

It would have been wise to omit all reference to exploratory puncture in appendicitis (p. 725) or to condemn it unreservedly.

There are many, assuredly, and among these is the reviewer, who will regret that in this otherwise excellent translation a somewhat prevalent but most unlovely fashion has been followed of omitting the terminal "al" from certain adjectives. Such adjectives as "cylindric," "anatomic," "tropic," "symmetric," "hysteric" and the like do not beautify or simplify the English language. But these are small criticisms of an excellent work—one of the best existing manuals of diagnosis.

THE EFFECTS OF CUTTING THE BRANCH OF THE HIS BUNDLE GOING TO THE LEFT VENTRICLE *

LEWELLYS F. BARKER, M.D., AND A. D. HIRSCHFELDER, M.D.
BALTIMORE

The idea that under certain conditions the two ventricles do not beat absolutely synchronously is an old one, and was used by C. J. B. Williams and by Skoda[1] to explain the production of split heart sounds. Experimental evidence of this asynchronism was given in 1890 by Philipp Knoll,[2] who showed that the right ventricle contracted before the left during vagus stimulation. Knoll's experiments were confirmed by Léon Fredericq[3] (1906) and his pupil Stassen[4] (1907). The latter showed that if ventricular extrasystoles were produced while the vagi were being stimulated, the ventricle in which the extrasystole was produced contracted 0.02 to 0.03 second before the other ventricle.

The idea that under certain conditions the action of the two ventricles might be so completely dissociated that a contraction of the one might be said to occur without the contraction of the other, was proposed by von Leyden[5] in 1868 to explain a case of arrhythmia, in which one small beat followed a few tenths of a second after the regular beats.

Von Leyden believed that the large beat corresponded to systole of one ventricle, the small beat to systole of the other. Indeed, his curves showed that, though the first of the two beats gave a larger impulse over the apex, the second of the two gave a larger impulse over the right ventricle. Von Leyden's explanation has been questioned by Riegel,[6]

* From the Medical Clinic of the Johns Hopkins Hospital and University.

1. Williams and Skoda, quoted from von Leyden.

2. Knoll, Philip: Ueber Incongruenz in der Thätigkeit der beiden Herzhälften. Sitzungsb. d. k. Akad. d. Wissensch. Math-naturw. Cl., Vienna, 1890, xcix, 31-53, 6.

3. Fredericq, Leon: La pulsation du cœur du chien est une onde de contraction, etc. Arch. internat. de physiol., 1906, iv, 60.

4. Stassen, M.: De l'ordre de succession des différentes phases de la pulsation cardiaque chez le chien. Arch. internat. de physiol., 1907, v, 600.

5. von Leyden, E.: Ueber ungleichzeitige Kontraction beider Ventrikel. Arch. f. path. Anat., 1868, xliv, 365.

6. Riegel, F.: Zur Lehre von der Herzirregularität und Inkongruenz in der Thätigkeit der beiden Herzhälften. Wiesbaden, 1891.

Hering,[7] Helsingius,[8] and a host of others who claim that the condition present was simply a pulsus bigeminus of extrasystolic origin. If this explanation is true, it would follow that over certain parts of the heart, especially over the right ventricle, the movement due to the extrasystoles was more marked than that due to the strong regular beat. This paradoxical effect might be due to the relation of the heart to the ventricle in the particular intercostal space during the extrasystole.

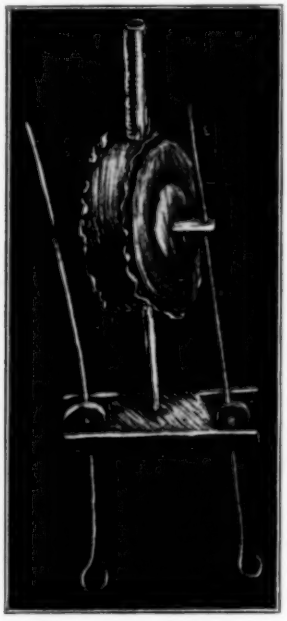


Fig. 1.—Air-transmission myocardiograph.

In 1907 Kraus and Nicolai[9] reported a case in which they believed that complete dissociation of the ventricles was present; and claim to

7. Hering, H. E.: Pseudo-Hemisystole und postmortale Hemisystole Deutsch. med. Wchnschr., 1903, xxix, 381.

8. Helsingius, O. F.: Zur Frage der Leydenschen Hemisystolie. Deutsch. med. Wchnschr., 1906, xxxii, 1406.

9. Kraus, F., and Nicolai, G. F.: Ueber das Elektrocardiogramm unter normalen und pathologischen Verhältnissen. Berl. Klin. Wchnschr., 1907, xliv, 765.

Ueber die funktionelle Solidaritat der beiden Herzhälften. Deutsch. med. Wchnschr., 1908, xxxiv, 1.

have shown it by electrocardiograms, though, as far as we know, they have not published the curves taken. In 1908 Hewlett[10] reported a case in which beats appeared on the jugular pulse which could not be seen on either the apex or the radial tracing. He believed that these curves on the jugular tracing represented systoles of the right ventricles unaccompanied by systoles of the left, and, moreover, notes that in many cases the interval between the cardiogram and jugular wave is subject to considerable variations.

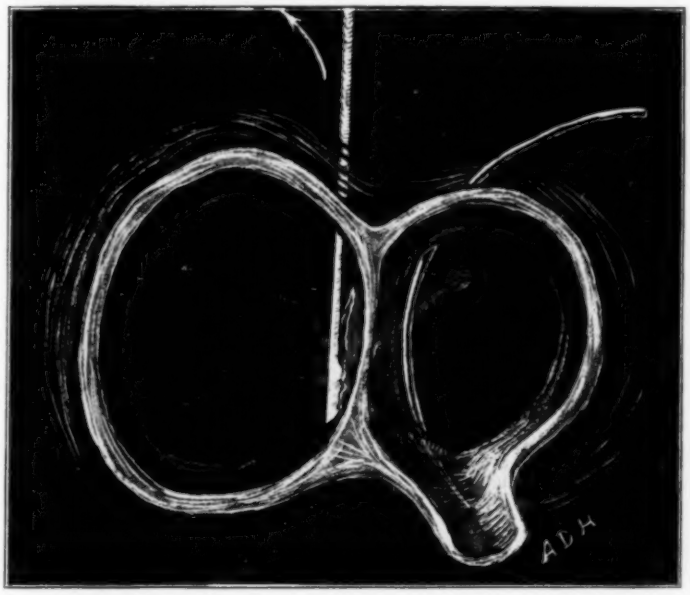


Fig. 2.—The ventricles viewed from above showing the curved needle inserted into the right ventricle and the knife blade cutting the bundle in the left. The atrio-ventricular bundle is shaded lighter than the rest of the heart muscle. The arrow shows the direction in which the knife handle is moved to make the cut.

We have found that curves bearing more or less resemblance to those published by Professor Hewlett may sometimes occur when the apex-beat disappears at the height of respiration, but Professor Hewlett has assured one of us that this will not explain many of the tracings which he has obtained.

10. Hewlett, A. W.: Heart-Block in the Ventricular Walls, THE ARCHIVES INT. MED., Chicago, 1908, ii, 139.

Schmoll,[11] in the same year, published an article entitled "Ataxia of the Heart Muscle," in which he carried the idea of incoördination one step farther and voices Wenckebach's view that "not the whole ventricle is contracting, but only certain parts of it." This explanation seems thus far devoid of physiological basis. MacCallum has shown that very large portions of the left ventricle can be thrown out of function by injection of alcohol into its substance without affecting the coördination of the chambers or even the blood pressure. On the other hand, the only definite experimental evidence of incoördination in the fibers of the ventricles is seen in the well-known phenomenon of fibrillary contractions, during which the circulation absolutely ceases and the blood pressure invariably falls at once to zero. Moreover, all of Schmoll's curves admit of interpretation in accordance with the well known types of phlebogram, without assuming an interventricular block.

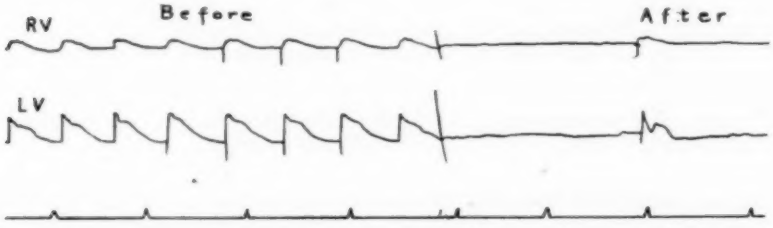


Fig. 3.—Contractions of right (RV) and left (LV) ventricles recorded by the myocardiographs before and after cutting the left branch of the atrio-ventricular bundle. Time in seconds.

The subject of interventricular heart-block, therefore, seemed worthy of experimental investigation. Several months prior to Hewlett's publication one of us had attempted to cut the left branch of the His bundle in the upper part of the ventricular system by introducing a knife through the wall of the ventricle and cutting into the septum, in the hope of blocking the cardiac impulse to the left ventricle but not to the right.

The number of experiments tried was too small to be conclusive, but no such incoordination was produced. During the past winter we attempted to carry on these experiments with an improved technic. The contractions of the ventricles were recorded by means of two myocardiographs. This apparatus (Fig. 1), made according to the suggestion of Dr. Dozier, of San Francisco, consisted of a double-ended tambour 2.5

11. Schmoll, E.: Ataxia of the Heart Muscle. Am. Jour. Med. Sc., 1908, cxxxvi, 663.

cm. in diameter, armed with two wire levers. The lower arms of the levers (2 cm. long) were hooked for insertion into the muscle of the ventricles, while the upper ends, above the fulcrum, were also 2 cm. long and passed through holes in a celluloid foot which was glued to the dam of the tambour. A small (0.3 mm.) brass tube led off from

Fig. 4.—The left ventricle showing the cut through all the ramifications of the left branch of the atrio-ventricular bundle, which appear lighter than the rest of the heart muscle.

the central myocardiograph tambour and was connected with the recording tambour by rubber tubing.

In the earlier experiments we attempted to cut the left branch of the His bundle with a firm knife-blade run into the ventricle through the

carotid artery and aorta. (During its passage the knife-blade was protected by a cardiac sound, from which it was then extruded.) This method was unsatisfactory, since it was difficult to do more than nick the walls of the septum.

A small knife-blade about 3 mm. in width was then used; it was introduced through the left wall of the ventricle as near as possible to the mid-line, and the septum was cut by a drawing stroke, pressing the handle of the knife to the left while drawing it toward the operator. In this way one successful operation was performed. However, after many partial cuts had been made, in which the anterior and posterior parts of the septum were nicked, but the middle portion of the septum left uninjured, it became evident that the interventricular septum must assume a concave form (with concavity toward the left) during systole. This was overcome by introducing a long curved needle into the anterior wall of the right ventricle as near as possible to the septum, following along the septum to the posterior wall, and penetrating the latter. The right ventricle was thus impaled on the curved needle and the concavity of the left aspect of the septum converted into a convexity (Fig. 2). When the knife-cut was now made as before it was much more often successful.

In all, fourteen operations were performed, in five of which the left branch of the His bundle was cut without injury to the right.

In all but one of the successful experiments this was followed by complete atrioventricular heart-block, but both ventricles contracted synchronously (Fig. 3). The rhythm was the slow, regular, independent ventricle rhythm. In these experiments several cuts were made, and the heart stopped beating after a few minutes, so that it can not be stated whether the complete block was due to the section of the branch and the trauma to the entire bundle, or was merely a terminal phenomenon.

In one experiment, however, in which only a single cut was made, the ventricular rate remained entirely unchanged and no block was present. The heart continued to beat vigorously even after removal from the body. The left branch of the Λ was cut through (Fig. 4), but the septum was not pierced and the right branch was absolutely intact (Fig. 5).

From the clinical and pathological side our experiments have the further confirmation that Saigo[12] found fatty degenerations and patches of myocarditis affecting the left branch of the bundle in many cases in

12. Saigo: Die Purkinjêschen Muskelfasern bei Erkrankungen des Myocards. Verhandl. d. deutsch. path. Gesellsch. Jena., 1908, xii, 165.

which the heart rate had been quite normal, and in which there had been no trace of ventricular incoordination.

It would appear, therefore, that the His bundle plays little if any rôle in the coordination of the two ventricles. This might be expected,

Fig. 5.—The right ventricle of the same heart, showing the septum and right branch of the atrio-ventricular bundle (indicated by the arrow) intact.

since Ludwig, Krehl, and MacCallum have shown that the fibers of one ventricle pass without interruption into those of the other. The muscu-

lar bridge between the two chambers is formed by the entire musculature of the heart wall, and hence there is no such narrow connection as is present between atria and ventricles at which a block might be produced. It seems more probable that any such incoordination, if present, would be between the different layers of muscle fibers common to the walls of both ventricles, rather than between the two ventricles themselves, and that in some cases of apparent hemisystole seen in animals just before the heart stops beating (and after the circulation has ceased) the outer layer of fibers in one ventricle has stopped beating, while the outer layer of the other (inner layer of the first) continues to beat for a few moments longer.

It is not our intention to claim that no such thing as a hemisystole ever occurs under clinical conditions, but merely that in the absence of experimental evidence of its occurrence a considerable degree of skepticism is warrantable. The experience of von Leyden demonstrates how easily a false interpretation of these phenomena may be made when founded on clinical observations alone.

We take great pleasure in expressing our thanks to Drs. George M. Bond and Elizabeth S. Hellweg for their kind assistance in these experiments.

6 East Franklin Street—2243 Linden Avenue.

EXPERIMENTAL PAROTITIS*

ISABELLA C. HERB, M.D.
CHICAGO

The most noteworthy study of the bacteriology of mumps is by Laveran and Catrin,[1] who in 1893 described a diplococcus in the exudate which they obtained by aspiration of the parotid gland. They found this diplococcus 67 times in 92 cases; 39 times the organism was obtained in pure culture, twice in mixed culture, and 15 times the result was negative. The 15 negative results they attribute to the small quantity of exudate obtained. In 16 cases of secondary orchitis pure culture was obtained 12 times, once with contamination and three times they obtained no growth. The organism was obtained from the blood during the height of the fever 10 times in 15 examinations. Three times pure cultures were obtained from the edema of the overlying tissue of the gland and once from the exudate of a joint. They found it fatal in large doses to white mice. Injections into the testicles of rabbits produced an inflammation which lasted about eight days.

In 1896 Mecray and Walch[2] examined the saliva from Steno's duct in 10 cases. They found a diplococcus 6 times. In 8 blood examinations they obtained the organism in pure culture 3 times, mixed with the white staphylococcus 3 times, and twice their results were negative. In the same year Busquet and Feri[3] examined the blood and saliva in 3 convalescents and in 17 patients during the early stages of the disease and found a diplococcus in all the cases.

In 1897 Michaelis and Biem[4] examined the secretion from Steno's duct in 16 cases and obtained pure cultures of a diplococcus in all. Their animal experiments gave negative results.

In 1906 Teissier and Esmein[5] examined the blood in 45 cases and obtained a diplococcus in 37. The negative results were in those with a light attack of the disease or during convalescence. The organism was

*From The Memorial Institute for Infectious Diseases, Chicago. This work was aided by grants from the American Medical Association. A preliminary report appeared in the Journal of the American Medical Association, 1908, li, 668.

1. Laveran and Catrin: Compt. rend. soc. de biol., 1893, v, 528.
2. Mecray and Walch: Med. Rec., 1896, i, 440.
3. Busquet and Feri: Rev. d. méd., 1896, xvi, 744.
4. Michaelis and Biem: Verhandl. XV. Cong. f. inn. Med., 1897, xv, 441.
5. Teissier and Esmein: Compt. rend. soc. de biol., 1906, lx, 803, 853, 897.

obtained 33 times in pure culture, twice with streptococci, twice with a bacillus and three times with a coccobacillus. The exudate from Steno's duct showed in 10 examinations 9 pure cultures. The coccus was fatal to guinea-pigs and rabbits. Following intraperitoneal inoculations an orchitis developed in 4 of 7 rabbits.

In 1907 Korentschewsky[6] isolated a diplococcus from the gland exudate in 21 of 29 cases. His blood examinations gave positive results in 8 of 32 cases. The organism was fatal to mice, guinea-pigs and rabbits in large doses. No results were obtained in dogs.

So far as may be judged from the description of the investigators I have cited it appears very probable that they have dealt with the same diplococcus.

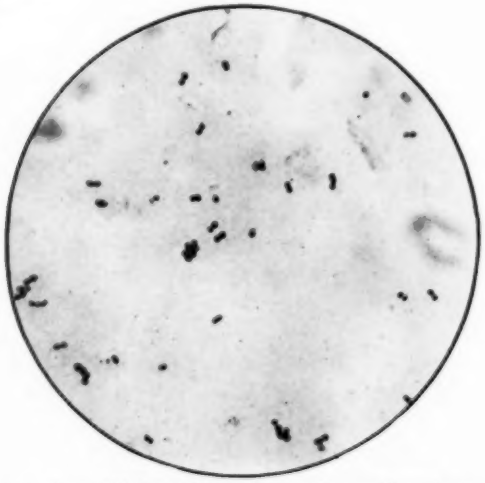


Fig. 1.—Smear from thirty-six-hour-old growth on glycerin agar. × 1200.

SOURCE AND DESCRIPTION OF DIPLOCOCCUS USED IN THE EXPERIMENTS

A similar diplococcus was obtained by me from the body of a man about 40 years old who entered the hospital in a moribund condition and died in a few hours. Except the report that he had had mumps no history was obtained. The postmortem by Dr. LeCount showed a right suppurative parotitis, bronchopneumonia and several minor lesions.

The cerebrospinal, pleural and pericardial fluids, bile, spleen, lung, testicle and right parotid gland were examined bacteriologically. Cover-

6. Korentschewsky: Centralbl. f. Bakteriol., 1907, xliv, 394.

glass preparations from the bile, pericardial and cerebrospinal fluids showed a rather large diplococcus; the latter also contained a small coccus occurring in groups. The pleural fluid contained a short bacillus. They were both Gram-positive. *Proteus vulgaris* was isolated from the pleural, cerebrospinal and pericardial fluids, the spleen, lung, testicle and parotid gland; *Staphylococcus albus* from the lung, testicle, cerebrospinal fluid and parotid gland. From the lung, testicle, cerebrospinal and pericardial fluids, bile and parotid gland a coccus was isolated with the following characteristics:

The coccus appears most frequently as a diplococcus, occasionally in chains of 4 to 6 elements, or in small groups (Fig. 1). It is round and

Fig. 2.—Uniform enlargement of the left parotid gland of dog on fourth day after injection of diplococcus into Steno's duct.

measures from 0.5 to 0.8 microns when about twenty-four hours old. When several days old it measures from 0.6 to 1.5 microns. It is easily stained by all the ordinary anilin dyes and is Gram-positive. It grows equally well aerobically and anaerobically. It is not motile, has no capsule or flagella and does not form spores, gas or indol. It grows best at 37 C.; 50 C. for three minutes destroys growth; cold inhibits but does not prevent growth when the culture is again placed under favorable conditions. Colonies developed from a milk culture two months old

and from agar which was dried till it was broken. While the coccus develops on all the ordinary media, its growth is characteristically slow, the twenty-four-hour glycerin agar colonies being scarcely visible.

Saliva being the natural secretion of the parotid gland, it was thought that the organism would grow more luxuriantly on a medium in which saliva was incorporated. This was found to be true, an abundant growth being obtained in half the time required on other media. Saliva was collected in test-tubes and passed through a porcelain filter (Pasteur-Chamberland). Nutrient agar-agar was heated to the melting point, allowed to cool to 48 C., and about ten drops of the sterile saliva added to an ordinary agar tube. The tube was then rapidly rolled between the hands in order to mix the agar and saliva

Fig. 3.—Showing parotid of same dog as represented in Figure 2, killed by chloroform on the fourth day after injection; skin and muscles have been removed.

thoroughly and solidified in the oblique position. The tubes were now incubated at 37 C. for forty-eight hours and carefully examined with a lens to make sure they were sterile before inoculating them. Sufficient saliva should be added to form some fluid of condensation.

Ascitic agar is also better medium than glycerin agar, but not so good as the saliva agar.

Glycerin Agar Stroke.—Pearly white, pin-point, discrete colonies without pigment.

Saliva Agar and Ascitic Agar Stroke.—Similar to glycerin agar but earlier and more abundant growth.

Human Blood Agar.—Pin-point, round, discrete colonies, surrounded by a clear white zone of hemolysis.

Blood Serum, Loeffler's.—Firm, white beaded growth without liquefaction of the medium or formation of pigment.

Potato.—Dull grayish-white, scanty growth without pigment.

Agar Stab.—Delicate beaded growth along line of puncture.

Glucose Agar.—Similar to plain agar. No gas.

Litmus Milk.—Soured in twenty-four hours; coagulated in forty-eight hours.

Plain Broth.—Slight clouding in twenty-four hours, later an abundant tenacious growth in the bottom of the tube.

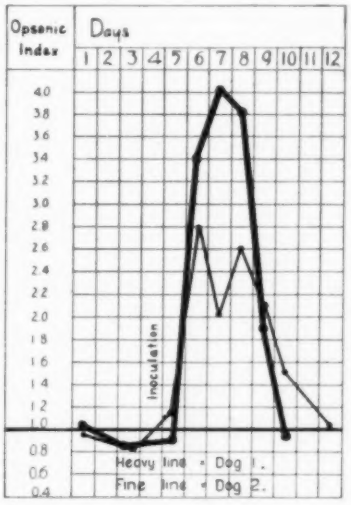


Fig. 4.—Chart of opsonic index in experimental mumps of dogs. (For history of Dog 1 see Experiment 2. The history of Dog 2 is not given.)

Gelatin.—Beaded growth along line of inoculation appearing about the third or fourth day with liquefaction of the medium in four or five weeks.

EXPERIMENTS

The organism is fatal to white mice, white rats, guinea-pigs and rabbits when injected subcutaneously or intraperitoneally. In the latter case the animals usually die within twenty-four hours of peritonitis. Those that survive for several days die of bacteriemia. The growth

from a forty-eight hour agar slant suspended in 1 c.c. normal salt solution injected into the testis of rabbits produces an acute inflammatory condition which lasts for seven to ten days and then disappears without suppuration, the structure later appearing perfectly normal. On the other hand, animals similarly inoculated with staphylococcus or streptococcus die of peritonitis within twenty hours, while an injection of normal salt solution alone produces no reaction.

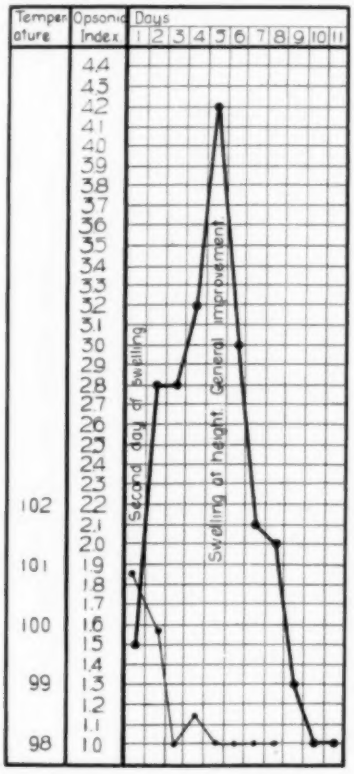


Fig. 5.—Chart of opsonic index for the diplococcus studied in a case of mumps.

The following experiment was made on a medium-sized so-called white-faced ringtail monkey:

Experiment 1.—On February 7 the animal (temperature 100.8 F.) was inoculated through the right Steno's duct with the growth from a forty-eight-hour ascitic agar slant suspended in 1 c.c. normal salt solution.

February 8: Temperature 103 F.: slight swelling of the parotid; refuses food.

February 9: Temperature, 103.2 F.; decided enlargement of the parotid; chews with difficulty, but does not appear sick.

February 10: Temperature 101.8 F.; parotid about as yesterday; less difficulty in chewing; appetite good.

February 11: Temperature, 101.2 F.; parotid smaller than yesterday.

February 12: Temperature, 100.8 F.; swelling of the parotid gradually disappearing.

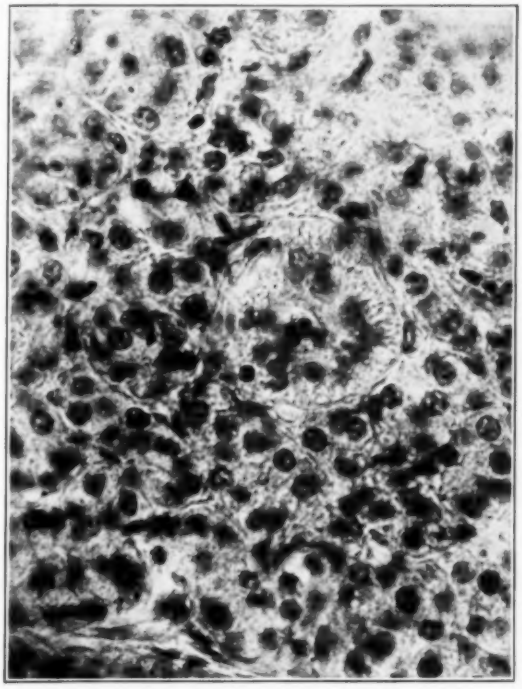


Fig. 6.—Section of the parotid of dog on second day after injection of the diplococcus into Steno's duct. × 650.

February 13: Temperature, 100.2 F.; swelling of parotid gradually disappearing.

February 14: Temperature, 100.2 F.; parotid appears of normal size.

Most of my experiments have been on dogs. In passing it may be noted that Busquet and Boudeaud[7] record an instance of mumps in the

7. Comp. rend. soc. de biol., lii, 675.

dog, a second animal getting the disease from the first. They isolated a "diplostreptococcus" from the saliva in Steno's duct in both dogs and from the blood of the second.

The dog seems to react in a characteristic manner to the introduction of the coccus I have studied into the parotid gland, while subcutaneous and intraperitoneal inoculations produce no results. Direct inoculation into the parotid gland of dogs causes a swelling of the gland, lasting for seven to ten days. The injection of suspensions into Steno's duct produces in dogs a uniform swelling of the parotid gland

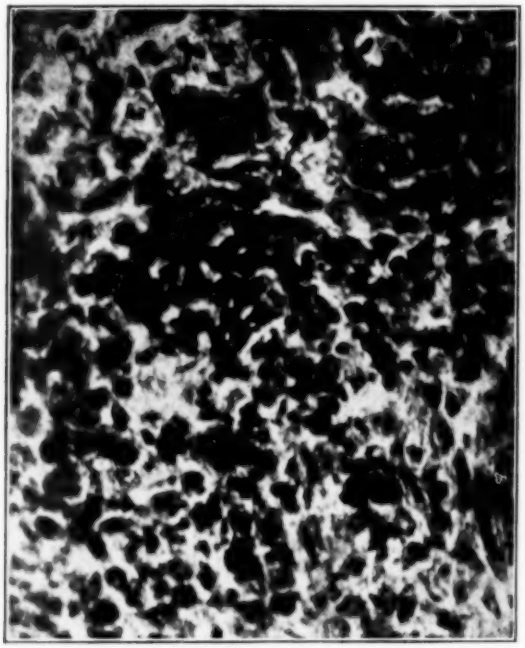


Fig. 7.—Section of the parotid on fifth day after injection. × 650

which begins in from 48 to 72 hours, continuing to enlarge for a few days, when the gland gradually returns to normal size. In these animals the temperaure during the period of the swelling of the gland ranges from 1 to 1.5 F. above normal; in no case did suppuration develop, and, with the exception of difficulty in chewing for a day or two, the animals appear to suffer no special inconvenience (Figs. 2 and 3).

Injections into the duct of mixed cultures of the organism and staphylococcus causes edema of that side of the face and the parotid gland in three or four hours and abscesses form in three or four days. In two dogs that survived these injections after drainage of the abscesses the parotid gland was completely destroyed. One dog died on the fifth day of bacteriemia; another developed lung abscesses and died on the twenty-third day.

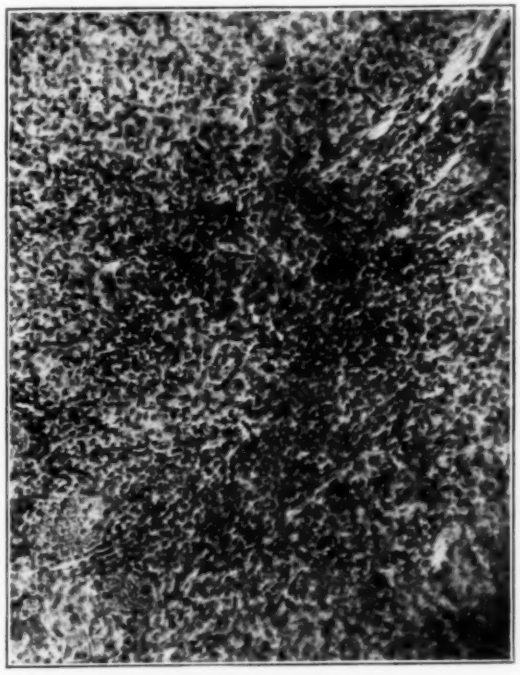


Fig. 8.—Section of the parotid on sixth day after injection. × 150.

The following records of experimental inoculations of the diplococcus into Steno's duct in the dog illustrates well the changes thus produced in this animal:

Experiment 2 (Dog 1).—February 24: Small, young black-and-white dog. Temperature, 102.5 F. Inoculated into the left Steno's duct with the bacteria from two forty-eight hour saliva agar slants suspended in 3 c.c. broth.

February 25: Temperature, 102.5 F. No visible change.

February 26: Temperature, 103 F. Parotid enlarged. Dog whines when firm pressure is made over the gland.

February 27: Temperature, 103.5 F. Parotid evenly enlarged and hard. Dog does not act ill, is playful and hungry, but experiences difficulty in chewing.

February 28: Temperature, 102.8 F. Gland about as it was yesterday. Pure cultures of the organism injected developed from aspirated fluid.

March 2: Temperature, 102.5 F. Swelling gradually disappearing.

March 5: Temperature 102.5 F. Almost no enlargement of the gland.

March 6: Temperature, 102.5 F. Gland appears normal.

For the opsonic index see chart (Fig. 4), heavy line.

Experiment 3 (Dog 7).—April 21: Large fox terrier (temperature 102 F.) was inoculated through the right Steno's duct with a forty-eight-hour growth from three tubes suspended in broth. Leucocyte count, 12,350.

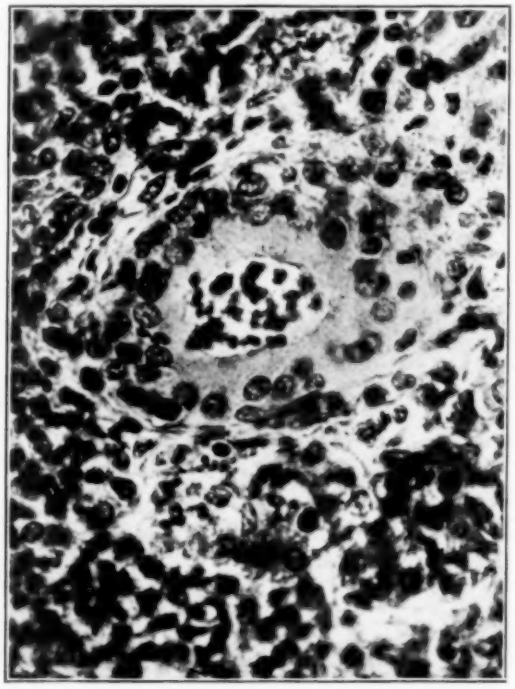


Fig. 9.—Section of the parotid on sixth day after injection. × 650.

April 22: Temperature, 103 F. Dog appears well. Leucocyte count, 12,350. Opsonic Index, 1.6.

April 23: Temperature 102 F. Dog shows swelling of parotid. Some difficulty in chewing. Leucocyte count, 31,200. Opsonic index, 1.2.

April 24: Temperature, 102. Parotid considerably larger than yesterday. Dog whines when pressure is made over gland. Difficulty in chewing. Testicles appear firmer and larger than normal. Leucocyte count, 31,000. Opsonic index, 2.2.

April 25: Temperature, 102 F. Parotid evenly enlarged and hard. Dog appears well and eats with less difficulty. Testicles about as they were yesterday. Leucocyte count, 30,000. Opsonic index, 2.

April 27: Temperature, 101.4 F. Parotid slightly decreased in size. Leucocyte count, 20,600. Opsonic index, 2.4.

April 28: Temperature, 101.8 F. Parotid smaller than yesterday. Leucocyte count, 23,700. Opsonic index, 1.9.

April 28: Temperature, 101.8 F. Parotid smaller than yesterday. Leucocyte count, 23,700. Opsonic index, 1.9.

April 29: Temperature, 102.5 F. Swelling of parotid rapidly disappearing. Leucocyte count, 10,400. Opsonic index, 1.4.

April 30: Temperature, 101.8 F. Parotid almost normal in size. Leucocyte count, 12,800. Opsonic index, 1.

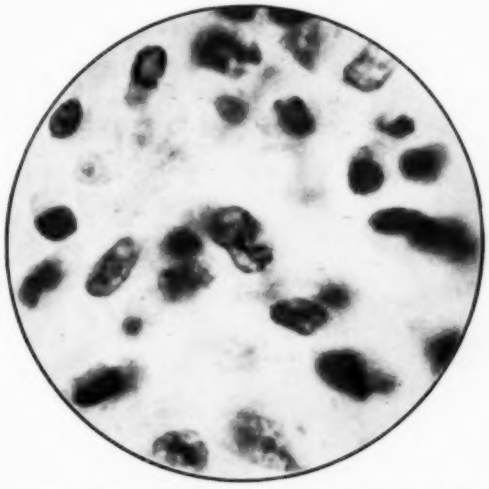


Fig. 10.—Section of the parotid on sixth day after injection. × 1250.

Unfortunately no differential leucocyte counts were made in this case. In other inoculated animals in which counts were made the same leucocytosis was observed and found to depend apparently on a uniform increase in the different forms of leucocytes. Sacquépée[8] found a moderate leucocytosis due to increase in the mononuclears in ordinary mumps without orchitis, while F. Pick[9] did not find any leucocytosis in mumps, but a relative increase in the mononuclears and a relative decrease in the polymorphonuclears.

8. Sacquépée. Arch. de méd. expér. et d'anat. path., 1902, iv, 114.
9. Pick, F.: Wien. klin. Wchnschr., 1902, xvi, 309.

Negative results were obtained in dogs inoculated through Steno's duct with filtrates of old broth cultures and suspensions of the diplococcus heated to 60 C. for 30 minutes. The opsonic index did not seem to be affected by these inoculations.

OPSONIC INDEX IN A CASE OF MUMPS

In spite of many efforts to secure opportunity to study cases of mumps during the progress of this investigation only one suitable case came under observation. The opsonic index of the serum of this patient for the diplococcus described in this report shows a well-marked rise at the period of the height of the swelling just as the temperature was returning to normal (Fig. 5). The clinical record follows:

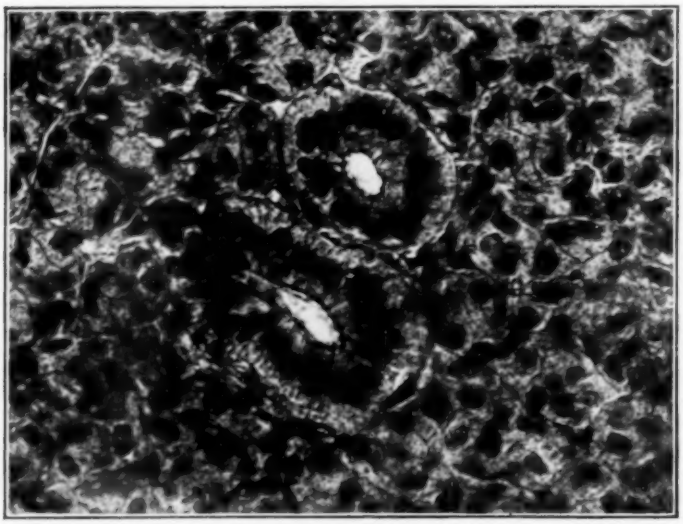


Fig. 11.—Section of parotid on tenth day after injection. Complete restitution. × 650.

Woman, aged 23, trained nurse, was caring for a child with mumps when she noticed (September 24) a swelling of the left side of the face.

September 25: Temperature 100 F. Swelling has increased and patient feels generally uncomfortable; has severe headache and difficulty in chewing.

September 26: Temperature, 99 F. Swelling of parotid and regional lymph glands quite marked. Head still aching; no appetite.

September 27: Temperature, 98 F. Parotid and regional lymph glands much enlarged and very hard. Some discomfort is felt when firm pressure is made over the parotid.

September 28: Temperature, 98 F. Is feeling better but no change in the swelling.

September 29: Temperature 97.6 F. No change in swelling.
September 30: Temperature, 98 F. Swelling seems less than yesterday. Feels well and is hungry.
October 1: Temperature, 98 F. Parotid and regional lymph glands decreasing in size.
October 2: Temperature, 98 F. Feels well. Swelling decreasing.
October 3: Temperature, 98 F. Swelling rapidly disappearing.
October 4: Temperature, 98 F. Swelling almost gone. Patient feels perfectly well.

GROSS AND MICROSCOPIC ANATOMY OF EXPERIMENTAL MUMPS IN DOGS

The enlarged parotid of inoculated dogs is of uniform firm consistency, the enlargement often reaching many times the normal size (Figs.

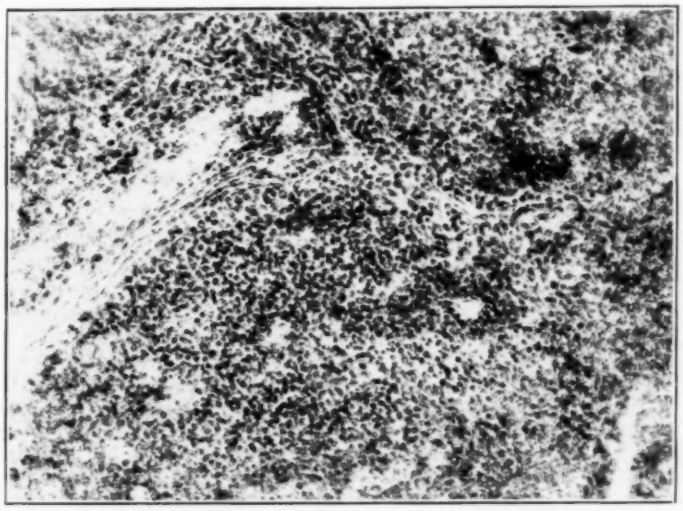


Fig. 12.—Section of cervical lymph of dog on seventh day after injection of the diplococcus into Steno's duct. × 150.

2 and 3): the cut surface is pinkish, exuding a little pinkish, rather turbid, fluid. The neighboring lymph nodes are moderately swollen, but there are no gross changes in other parts of the body.

Dogs inoculated through one or both Steno's ducts were chloroformed at various stages of the disease and sections made of the internal organs and bone marrow for microscopical study. In others the process was not disturbed and in these the blood changes were studied.

Pieces of tissue for microscopic study were removed immediately after the animals were killed and placed either in 85 per cent. alcohol

or Orth's fluid. Sections fixed in alcohol were embedded in paraffin, while those fixed in Orth's fluid were embedded in celloidin after being washed in running water for twenty-four hours. The femur was selected for the study of the marrow. The bone was sawed lengthwise and placed in alcohol. When the marrow was sufficiently fixed it was removed and embedded in paraffin. The marrow was stained with polychrome methylene blue and eosin, all the other tissues in hematoxylin and eosin.

Fig. 13.—Section of the testis of a dog on fourth day after injection of the diplococcus into Steno's duct. Cellular interstitial infiltration. × 150.

On the second or third day after inoculation there is a diffuse cellular infiltration of the interstitial tissue of the parotid which extended to the interlobular tissue to a slight extent. At the height of the swelling of the gland the cellular invasion has extended to the acini. The cells lining the ducts are swollen, occasionally desquamated, the lumen packed with cells and cell detritus. The ducts are the last to become

involved and the first to recover. The invading cells are composed of large polygonal cells with a vesicular nucleus, many containing small, dark chromatin granules or nuclear fragments, plasma cells, and a few lymphocytes and degenerated cells. By the end of the second week the gland has returned to normal condition. Suppuration or necrosis never occurred (Figs. 6-10).

The cervical and posttracheal lymph nodes show an early involvement. The capsule and trabeculæ contain distended vessels and there is

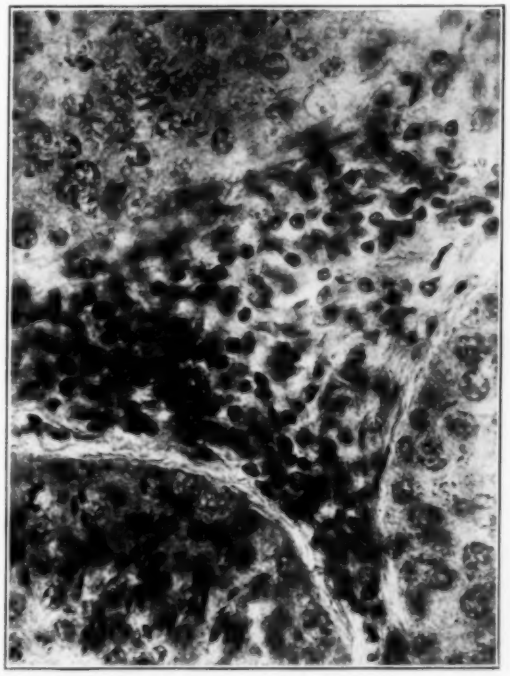


Fig. 14.—Section of testis illustrated by Fig. 13 at higher magnification. × 500.

more or less cellular infiltration. The lymph spaces are widened and filled with cells and the outline of the secondary follicles and medullary cords are indistinct (Fig. 12). In all the sections examined the cortical lymph nodes as a rule are difficult to define. The sinuses contain numerous large polygonal or elongated cells with a large vesicular nucleus, or a large, round nucleus with deeply staining chromatin granules,

increase in number of lymphocytes, phagocytic cells with two or more partly digested cells as also red blood cells and blood pigment.

In the sections of spleen examined the capillaries are distended with blood and there is increase in the large, round, granular mononuclear cells, leucocytes and small lymphocytes, nucleated red cells and large, marrow giant cells. In the spleen of one dog killed five days after inoculation there is a very marked increase in the nucleated red cells, which appear in clusters or groups of six or more. The follicles are swollen and contain numerous large polygonal cells with a vesicular nucleus.

In the bone marrow, so far as the comparatively few sections examined permit any statements, changes appear about the time the parotid begins to enlarge, but they disappear somewhat earlier than the parotid swelling subsides. There is a noticeable increase in the mononuclear cells, particularly in the neutrophilic myelocytes and the undifferentiated lymphocytes of Wolf, and also in the nucleated red cells. Slight increase in the megakaryocytes, eosinophiles and polymorphonuclear cells. These changes are most pronounced during the height of the infection.

An orchitis was present in one of the three male animals killed for microscopic examination. It is thought that this condition was present in some of the animals that recovered, as the glands appeared somewhat enlarged and firmer than normal. From a careful study of the material at hand (Figs. 13 and 14) it seems that the inflammation begins as a cellular infiltration in the intestinal tissue and soon invades the tubules. The cells forming the infiltration are of the mononuclear variety, the majority being polygonal cells with an eccentrically placed nucleus and a large amount of protoplasm; there are also cells with a uniformly densely staining eccentric nucleus, cells with a large vesicular nucleus and a small rim of protoplasm. About the time the invading cells penetrate the walls of the tubuli contorti there occurs a swelling and more or less indistinctness of the Sartoli and spermatogenic cells, with a cessation of mitosis in the spermatogenic cells. The spermatoids appear unaffected by the process. Unaltered spermatozoa are found in all the tubules except those most profoundly affected, in which they are absent. The cells lining the tubuli recti are swollen and the lumen is filled with desquamated cells and cell detritus. No areas of suppuration or necrosis were observed. The inflammatory changes consequently correspond to those which occur in the parotid.

About the time the parotid becomes enlarged the tubular epithelium of the kidney becomes swollen, cloudy, fatty and occasionally desqua-

mated. The lumen is more or less filled with granular material. Later there is an intense engorgement of the blood channels extending into the peripheral zones, about the fourth or fifth day after inoculation; cells are occasionally seen.

The pancreas, lung and suprarenals present no changes worthy of note.

The liver shows a slight cloudy swelling, with deposition of fat in the peripheral zones, about the fourth or fifth day after inoculation; later there is a marked congestion of the central and interlobular veins so that the liver cells are pressed into narrow bands. Small groups of mononuclear cells are present in the majority of sections.

SUMMARY

The principal, distinguishing or characteristic features of the diplococcus isolated from a case of mumps are the following:

Gelatin is very slowly liquefied. In broth a slight cloudiness is produced in twenty-four hours; later a tenacious deposit forms in the bottom of the tubes. Milk is soured in twenty-four hours and coagulated in forty-eight hours. Potato produces a grayish-white abundant growth. On blood agar a slight zone of hemolysis appears around the colonies. Agar cultures show pearly white, tenacious, pin-point, round, discrete colonies. No production of indol. The organism occurs most frequently as a diplococcus, occasionally in small groups or chains of from four to six elements. It is non-pyogenic.

When injected into Steno's duct in monkeys and dogs this diplococcus causes a diffuse non-suppurative parotitis, the infiltration being composed largely of mononuclear cells, and occasionally also orchitis of a similar character. During the course of this experimental parotitis the opsonic index for the diplococcus shows a marked rise, reaching the highest point at about the time when the parotid swelling is most marked. In one case of human mumps (the only one studied) a similar rise of the opsonic index for this organism took place. There is consequently good reason to regard this diplococcus, which corresponds well with the description given by Laveran and Catrin of the diplococcus isolated by them from cases of mumps, as the actual cause of mumps and the disease produced in my dogs as genuine experimental mumps.

CERTAIN UNUSUAL LESIONS OF THE LYMPHATIC APPARATUS

INCLUDING A DESCRIPTION OF PRIMARY HODGKIN'S DISEASE OF THE SPLEEN AND A CASE OF GASTROINTESTINAL PSEUDOLEUKEMIA*

DOUGLAS SYMMERS
NEW YORK

In 1832 Hodgkin[1] called attention to the existence of a disease characterized primarily by progressive enlargement of the lymph nodes and associated, in many instances, with enlargement of the spleen. In the light of our present knowledge it appears that several of the cases originally described by Hodgkin were examples of leukemia or of glandular syphilis or tuberculosis, but that at least two were genuine instances of the affection to which Wilks,[2] in 1856, gave the name of Hodgkin's disease and for which, in recent years, a definite histology has been established. Since the appearance of Wilks's paper in England, and a communication by Bonfils in France in the same year, many contributions have been made to the literature of the subject, and undoubtedly several different lesions have been described under the title of "Hodgkin's disease"; among them leukemia, non-caseous glandular tuberculosis, lymphosarcoma and pseudoleukemia. Despite the confusion occasioned by lack of knowledge of the pathologic histology of Hodgkin's disease, the older observers came to recognize two types, and to regard them as different varieties of the same lesion—one soft and characterized by great cellular richness, the other firm and tending to become sclerotic. Indeed, in the latter type, giant cells were observed by Virchow in 1864 and by Langhans in 1872. Perhaps the first important step in the elucidation of a problem which is still beset by many difficulties was accomplished by Virchow when he established the independence of leukemia. Shortly thereafter a further advance was made by Cohnheim,[3] who, under the title of pseudoleukemia,[4] described a case which

*From the Pathological Laboratory of the New York Hospital.

1. Hodgkin: Med. Chir. Tr., 1832, xvii, 68.
2. Wilks: Guy's Hosp. Rep., 1856, ii, 1865, xi, 56.
3. Cohnheim: Virchow's Arch. f. path. Anat., 1865, xxxiii, 451.
4. Cohnheim has been credited with the introduction of the term pseudoleukemia as a synonym for Hodgkin's disease, but, as a matter of fact, he employed it to describe a totally different affection, and in his original contribution did not once mention Hodgkin's disease, or otherwise add to the confusion of the subject.

presented the essential anatomical characteristics of leukemia without changes in the blood. Gradually other lesions were eliminated from the general category of Hodgkin's disease and were more properly classified elsewhere, so that in late years Hodgkin's disease appears to have been recognized as a definite histological entity, characterized by changes which resemble those of the infective granulomata. When fully developed these changes consist in proliferation of endothelial and reticular cells, the formation of giant cells, and progressive fibrosis, associated with variable numbers of lymphocytes and, in many instances at least, with plasma cells and eosinophiles, and were ably described by Sternberg[5] in a paper published under the title of "A Peculiar Form of Tuberculosis of the Lymphatic System." Other students of the disease have subscribed to the view that these changes are tuberculous or that they partake of the nature of tuberculosis.[6] Still others have denied the etiological relationship of the tubercle bacillus to Hodgkin's disease, partly because of negative results following the inoculation of animals and the administration of tuberculin in the living subject, and partly because of repeated failures to demonstrate the tubercle bacillus in microscopical preparations of the organs involved.

Practically all writers on the subject of Hodgkin's disease unite in declaring that the process almost invariably commences in the cervical or in anatomically related lymph nodes. Reed[7] even goes so far as to state that "we know of no case where the pathological anatomy was described in sufficient detail to permit of a positive diagnosis, in which the disease commenced elsewhere." Lyon,[8] in Osler's "Modern Medicine," states that there is no evidence that a primary splenic form of Hodgkin's disease exists. Simmons,[9] on the other hand, reports two cases of Hodgkin's disease that apparently commenced in the retroperitoneal lymph nodes, although no specific statement to this effect is made. In both instances enlarged nodes were present in the neck. In one case "a few small discrete glands were found in the posterior cervical triangle on both sides," while the retroperitoneal nodes formed a mass about 16 cm. in length and 7 cm. in diameter. In a second case there was a "discrete, freely movable gland in the right posterior cervical triangle

5. Sternberg: Centralbl. f. der Grenzgeb. d. Med. u. Chir., 1899, ii, 641, 711, 770, 813, 847.

6. Ferrari and Cominotti: Wien. klin. Rundschau, 1900, xiv, 1035. Crowder: New York Med. Jour., 1900, lxxii, 445. See discussion of Longcope's paper by Pearce and Ewing: Tr. New York Path. Soc., 1908, viii, 153.

7. Reed: Johns Hopkins Hosp. Rep., 1902, x, 133.

8. Lyon: Osler's Modern Medicine, ed. 1, Phila., Lea & Febiger, 765.

9. Simmons: Jour. Med. Research, 1903, ix, 378.

just above the clavicle, the size of a hen's egg," and several smaller ones on the opposite side. There were numbers of enlarged nodes in the abdomen, ranging in size from 2 to 7 cm. In the latter case, however, we are left in some doubt concerning the primary focus of the disease, since neither the clinical history nor the autopsy protocol is sufficiently specific to dispel the suspicion that the cervical involvement was primary. Longcope,[10] however, has adequately described a case of Hodgkin's disease that originated in the retroperitoneal lymph nodes. The patient was an emaciated man, 34 years of age, who, during life, presented signs of enlargement of the spleen and a moderate degree of anemia, together with elevation of temperature. There were no enlarged nodes in the neck. The skin and scleræ were jaundiced. At autopsy the retroperitoneal lymph nodes were enlarged and the common bile duct was surrounded and compressed by nodular masses lying just below the entrance of the cystic duct.

In the present communication I shall present the clinical and anatomical details of three cases of primary abdominal Hodgkin's disease, one originating in the spleen, the other two commencing in the retroperitoneal lymph nodes. At the same time I purpose to describe a remarkable case of pseudoleukemia in which practically the entire lymphoid apparatus, including that of the gastrointestinal tract, revealed the lesions of a generalized lymphomatosis and, in this connection, to emphasize the distinction between pseudoleukemia and Hodgkin's disease.

HODGKIN'S DISEASE

CASE 1.—Primary Hodgkin's disease of the spleen. M. V., aged 18, single, corset-maker, Belgian. Admitted to the New York Hospital, June 1, 1908; died June 30, 1908.

History.—The patient stated that three years before admission to the hospital she had passed several blood clots per rectum. At about the same time she observed that there was a mass in the abdomen. For two or three years previously, however, she had noted that the circumference of her waist was increasing. Four months before entering the hospital she began to experience irregularly recurring chills alternating with fever, sometimes two or three times in the course of a day. Latterly the ingestion of food has frequently been followed by vomiting, attended by generalized abdominal pains. She never noticed the presence of blood in the vomited matter. During the month that the patient was under observation the evening temperature rose on several occasions to 100 F. or 101 F.

Blood Count—
Red cells, 4,684,000.
White cells, 7,000.
Color index, 0.74.

10. Longcope: Bull. Ayer Clin. Lab. Pennsylvania Hosp., 1903, i, 4.

Differential Leucocyte Count—

Polynuclear leucocytes, 85 per cent.
Small lymphocytes, 11 per cent.
Large lymphocytes, 4 per cent.

No malarial organisms were detected in the patient's blood.

Physical examination revealed a well-nourished woman. The area of splenic dulness extended from the seventh rib on the left side to a point three inches below the umbilicus. The edge of the organ was palpable 1 inch above Poupart's ligament on the left side, whence it could be traced upward and to the right 2½ inches beyond the umbilicus, thence directly upward to the ensiform cartilage. The superficial lymph nodes were not enlarged.

On June 29 Dr. Hartley removed the spleen through a vertical incision in the left rectus muscle. The patient died the following day. At the operation no enlarged abdominal nodes were observed. No autopsy was obtained.

Anatomical Description.—The specimen consisted of a spleen 25 cm. in length, 18 cm. in breadth and about 8 cm. in thickness. The shape of the organ was well preserved. The capsule was diffusely, but moderately, thickened and the surface presented a diffusely grayish-red color. On section, the consistence of the organ was considerably increased and yielded a fine grating sensation when crushed between the fingers. The substance of the spleen was grayish-red in color and scattered through it were innumerable minute connective tissue strands. The Malpighian bodies were not visible. The cut ends of the vessels appeared to be thickened.

Two c.c. of an emulsion of the spleen in sterile bouillon were injected into the peritoneal cavity of a guinea-pig with negative results.

Microscopical Examination.—The lymphoid follicles were exceedingly few in number, not very rich in cells, and diffusely outlined. In most instances they were surrounded by delicate connective tissue fibrils arranged somewhat concentrically. In the center of the follicles the remains of obliterated blood vessels were apparent and, in the immediate vicinity of these, the lymphoid cells were densely packed. At the periphery of the follicles the lymphoid cells were scanty in number and loosely arranged and were gradually lost in the interstices of the connective tissue strands by which the follicles were surrounded. Between the follicles the substance of the organ was diffusely permeated by delicate connective tissue fibrils, frequently arranged in the form of slit-like apertures lined by endothelial cells. In the lining endothelium mitotic figures were occasionally to be seen. Most of the sinuses were empty; others were partly filled by endothelial and lymphoid cells and red blood corpuscles. Lying in many of the sinuses and almost or completely filling them were multinucleated giant cells which were provided with an abundance of pinkish, homogeneous or finely granular cytoplasm. In some of the giant cells the nuclei were small and fairly uniform in outline and lay heaped up in the center of the cell body. In others the nuclei varied in shape and size, and in chromatic richness, and presented evidences of fragmentation in the form of deep indentations. These giant cells were evidently derived from the endothelium of the sinuses, the nuclei apparently attempting at first to divide by karyokinesis and later resorting to a process comparable to simple fragmentation. Eosinophiles were unusually abundant. There were no evidences of necrosis.

This case represents, in my opinion, an example of primary Hodgkin's disease of the spleen and is remarkable from the standpoint of origin only. I have not been able to find an exactly similar case in the

literature. Donhauser[11] recently has reported a case of splenomegaly occurring in association with tuberculosis of the mesenteric lymph nodes and sclerosis of the bone marrow, in which the microscopical examination of the spleen bore a resemblance to that just described, in that there was considerable hyperplasia of the interstitial connective tis-

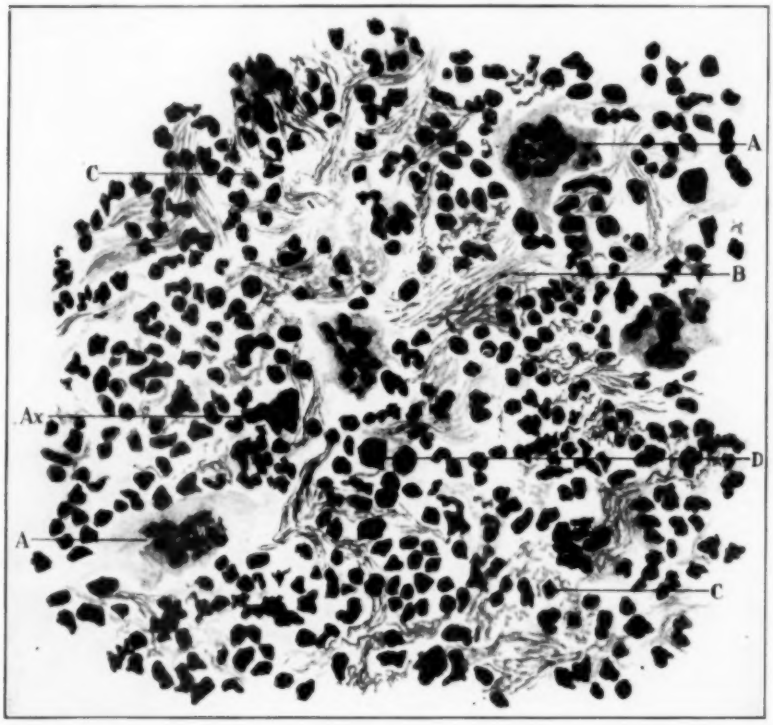


Fig. 1.—Primary Hodgkin's disease of the spleen, specimen from Case 1: A, giant cells; Ax, shows the early formation of giant cells, probably of endothelial origin; B, areas of fibrosis; C, eosinophiles; D, endothelial cells. Drawn with Edinger's apparatus.

sue, together with atrophy of the follicles and an occasional multinucleated giant cell. In addition, however, the spleen presented to the naked eye numbers of large and small, circumscribed, spherical nodules

11. Donhauser: Bull. Ayer Clin. Lab. Pennsylvania Hosp., 1908, v. 46.

which, on microscopical examination, were found to represent islands of hemopoietic tissue.

CASE 2.—Primary Hodgkin's disease of the retroperitoneal lymph nodes, secondary granulomatous lymphomata in the liver, kidney, spleen and bone marrow. L. G. B., male, white, aged 31, admitted to the New York Hospital October 19; died Oct. 30, 1904.

History.—The patient sought admission to the hospital because of progressive loss of flesh and strength. He stated that his illness began fourteen months before, with symptoms which led his physician to treat him for malaria. Two months before admission the patient's abdomen began to enlarge. Seven weeks later about two gallons of fluid were withdrawn. During the eleven days that the patient was under observation the evening temperature varied between 100 and 101 F.

Physical examination revealed marked emaciation, with pallor of the visible mucous membranes. The superficial veins over the abdomen were enlarged and the abdomen was distended by fluid.

Blood Count—

Red cells, 2,574,000.
White cells, 10,000.
Hemoglobin, 65 per cent.

Differential Leucocyte Count—

Polynuclear leucocytes, 84 per cent.
Small lymphocytes, 15 per cent.
Large lymphocytes, 1 per cent.

The superficial lymph nodes were not palpable.

On October 20 the abdomen was opened by median incision and 8 pints of clear yellow fluid escaped. Enlarged glandular masses were observed at the hilum of the liver and in the gastrohepatic omentum. Four days later the patient died after almost constant hiccoughs.

Abbreviated Autopsy Protocol.—Inspection: The body was markedly emaciated. On opening the peritoneum a small amount of fibrinous exudate was found near the lower end of the wound.

Chest: Negative.

Spleen: The spleen was somewhat flattened between the stomach and the left lateral abdominal wall and was increased to twice the normal size. The organ was reddish in color and moderately firm in consistence. Scattered over the surface were a few grayish bodies from 1 to 3 mm. in diameter.

Kidneys: Size increased. Capsules not adherent, cortices thickened, cortical markings coarse and indistinct.

Liver: Decreased in size, reddish in color, firm in consistence. The surface presented several capsular cicatrices from 0.75 cm. to 1.25 cm. in diameter. The general surface was irregular. On section the lobules were indistinct and a few grayish masses from 2 to 5 mm. in diameter were found scattered through the substance of the organ.

Stomach: Strong fibrous adhesions passed from the under surface of the liver to the hepatic flexure of the colon and to the stomach and first part of the duodenum. The stomach showed nothing unusual except that the pylorus was slightly thickened. There was no suggestion of a new growth. The pylorus looked upward and entered the concavity of a loop of intestine. This appearance was due to dilatation of the first part of the duodenum, owing partly to fibrous adhesions to the liver and partly to the presence of an enlarged lymph node opposite the head of the pancreas.

Lymph Nodes: The retroperitoneal lymph nodes in the upper part of the abdomen formed a large, grayish mass made up of numbers of nodes varying in size from 1 to 2 cm. These nodes were discrete and moderately firm in consistence. There was a single enlarged node in the lesser omentum that measured 3 by 1.5 cm. The mesenteric nodes presented no noteworthy naked-eye changes.

Microscopic Examination.—Spleen: The normal structure of the spleen was largely replaced by the overgrowth of delicate connective tissue fibrils, scattered through the interstices of which were small numbers of lymphoid cells and numerous multinucleated giant cells, by large masses of hyaline connective tissue supporting still larger numbers of giant cells of the same type and by areas of

Fig. 2.—Portion of large intestine from case of gastrointestinal pseudoleukemia (Case 4), showing wide-spread hyperplasia of the lymphoid follicles.

anemic necrosis. Eosinophiles were entirely wanting. The lymphoid follicles were markedly atrophied.

Lymph Nodes: Here, too, the normal structure was similarly replaced by the overgrowth of new tissue, so that it was impossible to distinguish cortical follicles, medullary cords or lymph sinuses. The framework of the node was made up of interlacing fibrils of connective tissue, among which were a few lymphoid and plasma cells and a large number of giant cells, some of which enclosed a single large nucleus, others multiple nuclei. Eosinophiles were not found. Areas of necrosis were visible here and there.

Liver: In the liver the normal architecture was irregularly replaced by masses of tissue corresponding in all essentials to those already described in the spleen and lymph nodes. The main features in the evolution of the new tissue which was destined to replace the liver parenchyma could be readily traced. The earliest observable change consisted in the occurrence of small lymphomatous foci lying in the adventitia of the portal vessels. These foci gradually increased in size and cellular richness, invaded the perilobular connective tissue and finally encroached on adjacent liver cells, pushing them aside and infiltrating the intercolumnar capillaries. As the focus enlarged, minute connective tissue fibrils began to appear among the lymphoid cells and to form a supporting network for them, while large, oval or rounded cells with prominent vesicular nuclei and pinkish, finely granular cytoplasm could be observed here and there. In some instances, these latter cells were provided with delicate cytoplasmic processes. Eventually the liver lobules were invaded irregularly and replaced by masses of tissue made up of a delicately reticulated connective tissue network supporting large numbers of endothelioid and epithelioid cells and multinucleated giant cells. In other instances the liver lobules were destroyed and transformed into enormous necrotic foci, in some of which large hemorrhagic extravasations were visible.

Kidney: Microscopical examination revealed marked granular degeneration of the epithelium of the convoluted tubules and the presence of hyaline casts. In the medulla, however, the picture was entirely different. Here the connective tissue supporting the blood vessels and straight tubules was richly infiltrated by lymphoid and plasma cells, the two varieties being present in about equal proportions. Among them were large numbers of typical multinucleated giant cells.

Bone Marrow: The bone marrow revealed the presence of masses of tissue that showed essentially the same structure as those already described in the spleen, liver and lymph nodes; that is, there were numbers of lymphoid, epithelioid and giant cells, enclosed in a network of connective tissue.

Aside from the fact that this case is an example of primary Hodgkin's disease of the retroperitoneal lymph nodes without cervical involvement, it is interesting from the standpoint of the histogenesis of the secondary visceral lesions, since the changes described in the liver indicate that the granulomatous masses are represented primarily by collections of lymphoid cells and that the other changes are sequential. In this connection another observation may be of interest. For example, a boy 16 years of age, presented himself at the New York Hospital in 1907, complaining of an enormous mass on the right side of the neck. A piece was excised for microscopical examination and was found to present the characteristic granulomatous lesions of Hodgkin's disease. A year later the boy returned to the hospital and a small lymph node was removed from the edge of the original growth. On microscopical examination this was found to present no changes on which the diagnosis of Hodgkin's disease could be based. On the contrary, the node presented the changes incident to diffuse lymphoid hyperplasia with proliferation of the cortical follicles. This tends to support the assumption that in the lymph nodes the initial manifestation of Hodgkin's disease consists in diffuse hyperplasia of the lymphoid cells, and that exhaustion

of these cells is accompanied or followed by connective tissue replacement and the other characteristic changes of the granulomatous lesion, to which reference has already been made.

The histological observations just mentioned are in accord with Longcope's conclusion[10] that Hodgkin's disease is conceived in hyperplasia of lymphoid cells; that lymph nodes are being constantly regenerated in the course of the disease, and that these structures ultimately become the seat of granulomatous changes.

CASE 3.—Primary Hodgkin's disease of the lymph nodes at the hilum of the liver. E. W., Hebrew, single, aged 20, admitted to the New York Hospital April 25, 1908; discharged June 1, 1908.

History.—On entering the hospital the patient stated that six weeks previously he began to experience sharp, lancinating pains in the right upper quadrant of the abdomen. These pains, although fairly constant, were worse at night and interfered with sleep. They continued for two weeks and then disappeared entirely, only to return four weeks later, when he sought admission to the hospital.

Physical examination revealed a poorly nourished boy, whose visible mucous membranes were blanched. The conjunctivæ were faintly jaundiced. There was slight bulging in the lower part of the chest on the right side in front, and some tenderness and muscular rigidity in the right upper quadrant of the abdomen. A rounded mass was palpated 3 cm. below the right costal margin and 1 cm. below the edge of the liver, which was likewise felt. The mass appeared smooth to the touch and moved with respiration. No pain was experienced by the patient when the right costal margin was forcibly depressed. The spleen was not felt. The superficial lymph nodes were not enlarged. During the five weeks that the patient was under observation the evening temperature was practically always from 100 to 102 F.

Blood Count—

White cells, 7,800.

Hemoglobin, 80 per cent.

Differential Leucocyte Count—

Polynuclear leucocytes, 70 per cent.

Small lymphocytes, 22 per cent.

Large lymphocytes, 7 per cent.

Eosinophiles, 1 per cent.

The urine was negative, except for the presence of urobilin.

The patient was transferred to the surgical side and operated on by Dr. Johnson. An incision 5 inches in length was made through the right rectus muscle. On opening the peritoneum a solid ovoidal mass about the size of a grapefruit was found projecting beneath the liver. It was not attached to the liver, gall bladder, adrenal or kidney, but rested in a bed beneath the liver. The mass was removed.

The surgical wound healed well and the patient eventually was referred to the Convalescent Home at White Plains.

Anatomical Description.—The specimen consisted of a large, heavy, ovoidal mass, 14 cm. in length and about 10 cm. in diameter. It was covered by a loosely

adherent connective tissue sheath, running through which were several large venous channels. The mass was very firm in consistence, faintly yellowish or cream-colored, and the surface was smooth. On section it cut firmly and the cut surface presented a yellowish translucent appearance and was faintly undulating. Scattered over the cut surface, at remote intervals, were small hemorrhagic areas, together with aggregations of pin-point-sized, rounded, yellowish elevations, separated from one another by delicate depressions. Running over the cut surface in different directions were coarse, pale, glistening, connective tissue bands.

Microscopical Examination.—Numerous sections were prepared from different parts of the mass. It was found that the structure of the lymph node was not recognizable, but had been replaced by the growth of dense bands of hyaline connective tissue, enclosing cellular islands of various shapes and sizes. The picture was further confused by the presence of large necrotic foci and hemorrhagic extravasations. In the connective tissue bands were a few scattered lymphoid cells, multinucleated giant cells and collections of eosinophiles. The more cellular areas differed somewhat from one another in composition. In practically every instance, however, cells of the fibroblastic type were so disposed as to form a more or less coarsely reticulated hyaline network, supported in the meshes of which were variable numbers of lymphoid cells, eosinophiles and multinucleated giant cells, together with enormous numbers of large flattened cells with large richly chromatic nuclei. These were evidently endothelial cells and the progenitors of the multinucleated giant cells. In several instances dense hyaline connective tissue bands were seen, which enclosed very small islands of tissue that bore a resemblance to tubercles, in that they were composed of somewhat concentrically arranged connective tissue fibrillæ with cytoplasmic processes which intercommunicated or were fused together, thus forming a network in which were numbers of lymphoid cells. Lying at the center, in most of these tubercle-like structures was a single giant cell with hyaline cell body and multiple nuclear fragments heaped up in the center, and provided at its periphery with delicate filamentous processes. These giant cells were surrounded by a clear space, bridged over at intervals by the filamentous processes just referred to. No tubercle bacilli were found in these localities nor, in fact, in any other.

Immediately on receipt of the specimen from the operating room, frozen sections were made and the diagnosis of Hodgkin's disease was established. An emulsion from the original mass was then made in sterile bouillon, and of this 2 c.c. were injected into the peritoneal cavity of a guinea-pig. The results were negative.

In this case we are provided with still another example of primary abdominal Hodgkin's disease, manifested clinically by a large tumor-like mass, originating, probably, in the lymph nodes at the hilum of the liver. In addition to its interesting anatomical and histological features, the case is instructive from the standpoint of the surgeon.

PSEUDOLEUKEMIA

Shortly after Virchow described leukemia, Cohnheim[3] recorded a case which presented similar anatomical characteristics without changes in the blood. For this disease he suggested the name of "pseudo-leukemia." The patient was a man, aged 24, who suffered from anorexia,

vomiting and repeated attacks of epistasis. The leucocytes were considerably diminished in number and no abnormal forms were present. At autopsy the spleen was greatly increased in size, measuring 10 by 7 by 3.5 inches, and presented innumerable hyperplastic lymphoid follicles. The liver was increased in size and, on microscopical examination, disclosed the presence of lymphomatous foci in the neighborhood of the portal vessels. The kidneys were enormously enlarged and, on microscopical examination, the interstitial tissues were found to be richly infiltrated by lymphoid cells. The cervical, inguinal and retroperitoneal lymph nodes were hyperplastic. The gastrointestinal tract presented no noteworthy changes.

Nearly thirty years before the appearance of Cohnheim's paper, however, Briquet[12] had pictured a peculiar disease characterized by extensive hyperplasia of the lymphoid tissues in the gastrointestinal tract, and since then a few similar cases have been added to the literature. These also are undoubtedly examples of pseudoleukemia and will be touched in more detail later.

A case of this description recently came under observation at the New York Hospital and its clinical and anatomical features are presented below in some detail.

CASE 4.—Gastrointestinal pseudoleukemia. J. M. S., white, aged 42, single, porter. Admitted to the New York Hospital June 24, 1908; discharged June 26, 1908. Readmitted Dec. 31, 1908; died Jan. 1, 1909.

History.—One year before the date of the patient's first admission to the hospital he noticed a painless swelling on the left side of the neck. It gradually increased in size and was followed six months later by the appearance of a similar mass on the opposite side. Three months later the patient began to have three or four stools daily. The stools were watery and defecation was painless. In the course of the next three months the stools increased to fifteen or twenty daily, and at the end of this time the patient sought admission to the hospital because of loss of strength and flesh.

Physical examination revealed a poorly nourished adult male. The visible mucous membranes were pale, the teeth in poor condition, the gums infiltrated by pus. Both tonsils were enlarged, especially the left. In the left anterior triangle of the neck were two glandular enlargements, each the size of a large walnut. In the left posterior triangle was an enlarged gland the size of a hazel nut. A mass of about the same size was present beneath the angle of the lower jaw on the right side. A number of smaller nodules was present on both sides of the neck, lying between the larger ones just described. The subclavicular nodes on both sides were palpable. The axillary nodes were enlarged to the size of marbles. All of the nodes were painless, discrete and freely movable.

Blood Count—
Red cells, 5,240,000.
White cells, 11,000.
Hemoglobin, 80 per cent.
Color index, 0.8.

12. Briquet: Cuveilhier's Atlas, 1835-42, ii, 34.

Differential Leucocyte Count—

Polynuclear leucocytes, 72 per cent.
Small lymphocytes, 24 per cent.
Large lymphocytes, 3 per cent.
Eosinophiles, 1 per cent.

The patient's temperature on admission at 3 p. m. was 99 F., normal thereafter. Examination of the stools revealed the presence of blood. The urine was negative. At the end of forty-eight hours the patient was discharged at his own request.

About midnight of Dec. 31, 1908, the patient was admitted to the hospital *in extremis*, presenting the classical signs of acute peritonitis. He died a few hours later, so that it was not possible to obtain any information concerning his condition during the six months which had elapsed since he came first under observation. A blood examination at this time revealed a leucocytosis of 14,400 and a preponderance of polynuclear leucocytes. It is also interesting to note that just before death digital examination of the rectum was made by one of the house surgeons and numerous small nodules were felt scattered through the mucous membrane.

Abbreviated Autopsy Protocol.—The autopsy was performed four and a half hours postmortem.

Inspection: The body was that of a man 42 years of age, 170 cm. in height, of large, well-developed frame, poor musculature and nutrition. The skin and visible mucous membranes were very pale. In the region of the left parotid gland and extending downward into the neck was a globular swelling, half again as large as a hen's egg. This lay immediately beneath the skin, was elastic to the touch and freely movable. There was a similar but somewhat smaller mass just below the angle of the jaw on the right side. Beneath the skin covering the front of the chest were a few masses of like description, the largest of which was flattened and about the size and shape of the thumb nail. The skin over the anterior chest and over the lower aspect of both legs presented a number of pin-head-sized, hemorrhagic petechiæ.

Peritoneum: The abdomen contained a large quantity of cloudy fluid in which were numbers of gelatinous clots. The peritoneum was opaque and irregularly covered by fibrinous exudate. The intestinal loops were frequently matted together by fibrinous material, beneath which the serosa was opaque and irregularly injected.

Lungs: Emphysematous, otherwise entirely negative.

Spleen: The spleen measured 15 by 10 by 5 cm. The shape was well preserved. Seen through the capsule it presented a grayish-red color. The capsule was thin and tense. On section the organ cut firmly. The cut surface was pinkish in color. Scattered over the cut surface were innumerable large and small, rounded or irregularly outlined, pale, translucent bodies. These were arranged in close proximity to one another and the scanty amount of tissue between them was opaque and pinkish; thus the cut surface presented a coarsely speckled appearance. Some of the larger translucent bodies were intersected by delicate reddish lines. The consistence of the organ was noticeably increased, imparting a fine grating sensation when crushed between the fingers. Lying at the hilum were a half dozen lymph nodes, the largest of which measured 4 cm. in length and 1 cm. in thickness. The nodes were pale, discrete and elastic to the touch. On section, the cut surface was pale and sprinkled over with minute reddish points, thus giving the whole a unely mottled appearance.

Adrenals and Semilunar Ganglia: Negative.

Kidneys: These organs were considerably increased in size and presented the characteristic naked-eye appearance of an acute diffuse hemorrhagic nephritis.

Liver, Gall Bladder, Pancreas, Urinary Bladder, Abdominal and Thoracic Aortas, Prostate, Testicles and Ureters: Presented no noteworthy naked-eye changes.

Bone-Marrow: The marrow of the vertebræ was diffusely bluish-red in color.

Lymphoid Apparatus: The tongue, larynx, esophagus, thyroid gland, stomach, pancreas and liver were removed *en masse*, together with numbers of enlarged lymph nodes from the lateral region of the jaw on both sides and from the neck, thorax and abdomen. The tongue presented moderate numbers of hyperplastic lymphoid follicles at the base. Large numbers of tumor-like masses were removed from the region of the left parotid gland, from beneath the angle of the lower jaw on the right side, from the sides of the neck, esophagus and trachea as low down as the bifurcation of the latter. The peribronchial lymph nodes were markedly enlarged and faintly anthracotic. In these several situations the size of the individual nodes varied from that of a pea to a hen's egg. Many of the smaller nodes were entirely discrete. In other instances large numbers of nodes of varying dimensions were clustered to form masses the size of a child's fist. This was specially true of the upper cervical region. Each node was enclosed in a definite connective-tissue capsule which served to separate one from the other. On section, the nodules were moderately firm in consistence and presented a smooth, pale or faintly pinkish, homogeneous, glistening surface, intersected at the periphery, in occasional instances, by coarse, yellowish lines derived from the capsule. In many of the nodules minute reddish points could be seen here and there or faint reddish lines were visible running across the cut surface. The mesentery was enormously thickened through the presence in it of dozens of pale, rounded masses, each enclosed in a connective tissue capsule which separated them from each other and from the peritoneal covering of the mesentery. These nodes varied in size from a small marble to a crab-apple and, on section, presented essentially the same naked-eye appearance as those elsewhere described. At the hilum of the spleen were small numbers of enlarged, discrete lymph nodes. The pancreas was literally embedded in enlarged nodes, many of which were entirely discrete.

Stomach: The walls of the stomach were greatly thickened. The rugæ were unusually numerous and very prominent. Between them the mucous membrane presented vast numbers of pale, opaque, nodular masses, separated from one another by shallow crypts. In the pyloric region these nodules were still more numerous and prominent, where they appeared as discrete, rounded or conical, closely apposed elevations about 0.5 cm. in height. On section, they appeared to be limited to the mucosa and presented a pale, homogeneous surface.

Intestine: The walls of the intestine throughout were greatly thickened. The lumen of the intestine was large, the mucous membrane pale or cream-colored. Scattered through it, from the pyloric end of the stomach to the anus, were myriads of nodular masses of different sizes. These were arranged in such close proximity to one another that the intervening mucous membrane was scarcely visible. In the mucous membrane of the duodenum immense numbers of small, rounded nodules were separated from one another by small sheets of tissue made up of pin-head-sized follicles. In the jejunum the rugæ were exceedingly large. Distributed through the mucous membrane, lying partly along the summit of the rugæ and thickly dispersed through the mucosa between the rugæ, were hundreds of pale, nodular projections, varying from the size of the head of a pin to that of

a large pea. For the greater part these bodies were conical in shape and rested upon a broad base embedded in the mucous surface of the intestine; a few were attached by delicate pedicles and hung free in the lumen. Here and there these nodules were aggregated to form cauliflower-like excrescences from 2 to 4 mm. in height. Essentially the same general description applies to the mucous membrane of the ileum throughout its entire extent, except that the cauliflower-like excrescences were even more numerous, and hyperplastic Peyer's patches came into view. These latter bodies were present to the number of a dozen or more and were roughly quadrangular in outline and from 2 to 7 cm. in length and 2 to 4 mm. in height. The mucous membrane of the cecum presented a cream-colored, velvety appearance and was thrown into massive folds that were arranged more or less concentrically. At the commencement of the ascending colon was a pedunculated mass, 4 cm. in height, the surface of which was traversed by a few shallow furrows. The mucous membrane covering the mass was smooth and slate-colored. On section the cut surface of the mass was pinkish in color and smooth. In the mucous membrane of the large intestine, from the ileocecal valve to the anus, were literally thousands of closely aggregated, pale, rounded, nodular projections, varying in size from a millet-seed to a split pea. Many of them presented small crater-like depressions at the summit. In this part of the intestine the transverse folds of the mucous membrane were enormous and were capped by numbers of rounded nodules, many of which were deeply pigmented. The nodules lying in the mucous membrane between the folds were pale and thickly set together, so that the contrast between the rugæ and the intervening surface was very striking.

Anatomical Diagnosis.—Chronic sclerotic localized pericarditis; brown atrophy of heart; emphysema; lymphoid hyperplasia of spleen; chronic interstitial splenitis; acute diffuse exudative hemorrhagic nephritis; multiple angiomata of liver, stasis; acute diffuse purulent peritonitis; lymphoid hyperplasia at the base of the tongue; lymphomatosis of the cervical, thoracic and abdominal lymph nodes and of the gastrointestinal tract (pseudoleukemia).

Microscopical Examination.—Spleen: The lymphoid follicles were unusually numerous and varied in size within considerable limits. Most of them, however, were distinctly increased in size, rich in cells and definitely encircled by bands of delicately fibrillar connective tissue, enclosing within its meshes moderate numbers of lymphoid cells. In other instances the follicles were irregularly intersected by trabeculæ of fibrillar connective tissue that served to divide them into cellular islands of variable shapes and sizes. In still other places the follicles were very small and were surrounded by masses of loosely arranged connective tissue, that appeared to be closing in equally on all sides, thus tending to replace the follicle as a whole. That such a replacement was eventually effected at times was evidenced by the fact that here and there were rounded islands of tissue made up of a rather coarsely reticulated network, supporting focal collections of lymphoid cells. In still other instances the follicles were invaded and partially replaced by masses of connective tissue, supporting considerable numbers of slit-like apertures that were filled by red blood corpuscles. The vessels of the follicles practically everywhere were thickened and hyaline in appearance and their lumina were partially or completely obliterated. Between the various follicles the splenic pulp was extensively replaced by a delicate interlacement of connective tissue fibrillæ. The interstices between the individual fibrils contained considerable numbers of lymphoid cells; others were filled by red cells. The connective tissues also supported numerous small sinuses lined by endothelial cells. Most of these sinuses were occupied by lymphoid cells, others by red blood corpuscles.

TABULAR PRESENTATION OF CASES OF GASTROINTESTINAL PSEUDOLEUKEMIA

Case No.	Sex.	Age.	Superficial Lymph Nodes.	Abdominal Lymph Nodes.	Gastro-intestinal Tract.	Spleen.	Liver.	Blood.	Author. Reference.	Remarks.
1	M.	41	Hyperplasia of faucial and lingual tonsils and of inguinal lymph nodes.	Greatly enlarged.	Rugæ of stomach enormously thickened. Hyperplastic follicles and polypoid masses throughout small intestine. Peyer's patches in lower ileum enlarged. Polypoid and sessile follicles in large intestine. Appendix greatly thickened.	.....	.....	.....	Briquet[12].....	.....
2	F.	55	Cervical and inguinal nodes enlarged.	Mesenteric glands greatly enlarged.	Stomach studded over by large and small cream-colored, flattened tumors. Similar masses present in small intestine below duodenum. Solitary follicles and Peyer's patches greatly enlarged. Enormous fold-like thickening of mucous membrane of ileocecal valve.	Weight 1,320 gms. Follicles markedly hyperplastic.	.....	Red cells, 4,720,000; 4.3 white cells to 1000 red cells.	Carrington[16]. .	General wasting for 6 mos. No abdominal symptoms.
3	M.	54	Cervical, axillary and inguinal glands enlarged.	.....	Solitary lymphomatous nodules near pyloric end of stomach. Enlargement of solitary and agminated follicles from duodenum to anus.	Size 25×37.5 cm., studded with white nodules.	Solitary lymphomatous nodule.	.....	Hadden[17].....	Emaciation.
4	M.	48	Marked hyperplasia of faucial and lingual tonsils.	Mesenteric nodes enlarged.	Large polypoid, sessile and vermiform thickenings in stomach together with smaller raised, flattened nodules. Innumerable lymphomatous nodules in small gut. Peyer's patches enlarged. Colon free.	Weight 765 gm. Follicles markedly hyperplastic.	.....	.....	Pitt[18].....	.....
5	M.	62	General enlargement of superficial lymph nodes.	Enlarged. .	Polypoid masses and sinuous folds in stomach. Flattened elevated patches in small intestine throughout. Elevated patches and polypoid outgrowths in colon. Appendix greatly thickened.	Three times normal size. Follicles gleatly enlarged.	.....	Red cells, 2,100,000; Hb., 55 %. No leucocytosis.	Schlesinger[19].	.....

6	M.	50	Great enlargement of cervical glands. Nares filled by lymphomatous masses. Tonsils hyperplastic.	Greatly enlarged.	Stomach diffusely invaded by lymphomatous nodules. Enlarged follicles in esophagus. Solitary and agminated follicles throughout small intestine hyperplastic. Cecum filled by pigmented nodules. Appendix thickened and nodular. Follicles in colon enlarged.	Solitary lymphomatous nodule.	.....	.....	Herrick[20].....	Lymphomatous masses in the lungs.
7	F.	57	Hyperplasia of faucial and lingual tonsils and of cervical and inguinal nodes.	.....	Mucosa of stomach greatly thickened and thrown into folds. Pea-sized nodules between folds. Hyperplasia of solitary and agminated follicles of small gut and of follicles of colon.	Size 16×10×4 cm. Follicles enlarged.	.....	.....	Stoerck[21].....	Diarrhea alternating with constipation; blood in stools. Great abdominal pain.
8	M.	51	Universally but slightly enlarged.	Enlarged..	Mucous membrane of stomach diffusely thickened; in places nodular. Solitary follicles and Peyer's patches hyperplastic. Appendix thickened.	Enlarged. Follicles hyperplastic.	Numerous small foci; lymphomatous.	.....	Wells'[3] and Mayer.	Lymphomatous foci in esophagus, kidneys, pancreas, prostate and adrenals. Anemia, night sweats "poor digestion," prostration, tenderness in epigastrium.
9	M.	48	Right cervical nodes enlarged. Large mass in left inguinal region.	Perigastric and peripancreatic nodes enlarged.	Polypoid and nodular masses in stomach. Hyperplastic follicles in upper half of duodenum and throughout jejunum and ileum. Peyer's patches enlarged. Follicles in colon enlarged throughout. Fungoid mass in cecum.	Slightly enlarged. Follicles hyperplastic.	Numerous lymphomatous foci.	Leucocytes, 10,600.	Celler[15].....	Intussusception at ileocecal valve.
10	M.	42	Faucial and lingual tonsils enlarged. Cervical nodes on both sides.	Enlarged..	Enlargement of rugæ in stomach together with nodular masses. Nodular lymphomata from pylorus to anus. Polypoid masses in jejunum. Peyer's patches enormous. Large sinuous folds in cecum.	Markedly enlarged. Follicles very prominent.	Microscopic lymphomata.	Red cells, 5,240,000; leucocytes, 11,000. Hb., 80%.	Symmers.....	Purulent infiltration of gums; 15 to 20 bloody stools daily.
11	F.	..	Enlarged inguinal and cervical nodes.	Enlarged..	Thirty cm. of small intestine excised at operation and found studded with nodules. (Balance of gastro-intestinal tract not examined, but probably involved.) Peyer's patches enlarged. Several polypoid tumors in excised intestine.	Not enlarged.	.....	.....	Hoffman[14].....	Diarrhea persistent. Occasional vomiting Intussusception at ileocecal valve.

Liver: The only noteworthy microscopical change in the liver consisted in the occurrence of numbers of small, richly cellular lymphomatous foci, lying in the connective tissues of the periportal spaces and probably derived from the outer sheath of the portal veins.

Kidneys: The microscopical changes corresponded to those usually found in acute diffuse hemorrhagic nephritis.

Lymph Nodes: Numbers of microscopical preparations of nodes removed from various parts of the body were examined. All of them showed essentially the same changes. The normal architecture of the node was markedly altered, so that the distinction between cortex and medulla was entirely lost. Neither lymph follicles nor sinuses were distinguishable. The node was surrounded by a moderately thick connective-tissue capsule through which small numbers of lymphoid cells were dispersed. Connective-tissue trabeculæ, derived from the capsule, penetrated the node at different intervals and divided the substance of the organ into large, densely cellular islands of lymphoid tissue. Among the lymphoid cells were moderate numbers of large rounded cells with abundant pinkish cytoplasm. These cells were provided with a single large rounded or indented nucleus or, in some instances, with two or three nuclei. The connective tissue trabeculæ were broad and made up of exceedingly delicate, loosely woven fibrils, sprinkled through the meshes of which were relatively small numbers of lymphoid cells. The connective-tissue bands were dispersed through the substance of the node in a more or less regular fashion, and their pale, non-cellular appearance formed a striking contrast to the large, densely cellular lymphoid islands around which they were disposed. Microscopical examination of the discrete nodes described in the protocol as reddish in color or faintly speckled revealed a slightly modified picture. In these nodes large, densely packed masses of lymphoid cells were separated from one another by thin bands of coarsely reticulated connective tissue supporting numerous deeply injected vascular channels with thick, hyaline walls.

Intestine: Sections removed for microscopical examinations from the nodular areas in different parts of the intestine disclosed the presence of enormous lymphoid collections occupying the mucosa and submucosa, replacing and almost completely destroying the glandular elements. Arranged around the periphery of the individual nodules were numbers of small, circumscribed, richly cellular lymphoid foci that stood out in strong contrast to the interior or medullary substance, which was composed of loosely arranged, diffusely distributed lymphoid cells.

This case is interesting from several standpoints. In the first place, it presents certain clinical features that are suggestive of Hodgkin's disease, in that the initial visible manifestations of the process occurred in the cervical region in the form of slowly progressive glandular enlargements that were discrete, painless and freely movable beneath the skin. These were accompanied by advancing asthenia and cachexia and by the blood picture that is usually found in Hodgkin's disease; in fact, in the absence of a microscopical examination of the glandular masses during life, the case was actually regarded as one of Hodgkin's disease. Death occurred after the lapse of eighteen months and the anatomical distribution and naked-eye appearances of the enlarged glands fulfilled the requirements of Hodgkin's disease as seen at autopsy. The widespread lymphoid hyperplasia in the gastrointestinal tract, however, stood

out in marked contrast to all the known lesions of Hodgkin's disease. The absence of changes in the blood and of leukemic infiltration of the viscera served, among other things, to distinguish the disease at once from true leukemia. It remained, however, to classify the case with regard to its relation to pseudoleukemia as conceived by Cohnheim, and to the changes described by Sternberg as a peculiar form of lymphatic tuberculosis and later described in this country by Reed as a non-tuberculous lesion forming the sole histological basis of the clinical entity known as Hodgkin's disease. In this connection I think it has been made clear from the description of the histological changes that the case belongs in the former category and that it probably bears no relationship to Hodgkin's disease.

This case, too, while noteworthy, is not unique. Thus, in an extensive review of the literature, Wells and Mayer[13] were able to collect reports of seven cases of gastrointestinal pseudoleukemia in which the changes in the lymphoid tissues were no less remarkable than those just described. These observers added another case, and recently Hoffmann[14] and Celler[15] have each reported a case, so that the one described in the present paper brings the total number to eleven. I have attempted to collate the chief points of interest in all these cases and to present them in the accompanying table.

ANALYSIS OF TABLE

While the number of cases of gastrointestinal pseudoleukemia available for analysis is not sufficient to warrant general deductions, several interesting points of similarity are apparent.

Eight of the eleven cases occurred in males, the youngest subject being 41 years of age, the oldest 62.

In spite of the extensive anatomical alterations in the stomach and intestines, definite clinical symptoms referable to these changes are recorded in five instances only. Thus, in Stoerck's case, there was a history of diarrhea alternating with constipation, of bloody stools and abdominal pain. In Hoffman's case the patient complained of persistent diarrhea and vomited occasionally. In my own case there was a history of prolonged and severe diarrhea attended by blood in the stools. In Wells and Mayer's case there is an indefinite reference to digestive disturbances. In two cases intussusception occurred.

13. Wells and Mayer: Am. Jour. Med. Sc., 1904, cxxviii, 837.
14. Hoffman: Arch. f. klin. Chir., 1907, lxxxii, 794.
15. Celler: Tr. New York Path. Soc., 1908, viii, 148.

The anatomical picture, however, is more uniform. In practically every case the superficial lymphoid structures were more or less enlarged. Thus the faucial and lingual tonsils were enlarged in five cases, while hyperplasia of the superficial lymph nodes was almost constant, especially in the cervical region, being absent in one case only. The spleen was enlarged in eight instances, depending, apparently, on hyperplasia of the lymphoid follicles. In 4 cases small lymphomatous foci were present in the interlobular connective tissue of the liver.

In the gastrointestinal tract the changes varied both in extent and location. Great thickening of the walls of the stomach was practically constant and in most instances the mucous membrane was thrown into massive vermiform folds. Between the folds the lymphoid tissues were markedly hyperplastic, appearing as nodular masses or as polypoid projections. In the intestine the duodenum presented more or less marked evidence of lymphoid hyperplasia in seven cases. Similar but more extensive changes were constant in the jejunum, where polypoid masses frequently were encountered. Widespread hyperplasia of Peyer's patches was a constant feature. In four instances the appendix was markedly thickened. In two cases the mucous membrane of the cecum was thrown into large sinuous folds. Lymphoid hyperplasia of the follicles in the large intestine was present in nine cases, most often in the form of discrete nodules, but sometimes in the form of polypoid outgrowths. In nine instances the abdominal lymph nodes were enlarged, sometimes to an enormous extent.

SUMMARY AND CONCLUSIONS

1. Whether Sternberg be correct in his contention that the changes in Hodgkin's disease are tuberculous is a problem with which this paper is not directly concerned, but, in view of the doubtful etiology of the disease and the several synonyms which have been incorrectly applied, it seems desirable, in the light of the specific histology which has been established for the process, to coin some term which will describe its microscopical peculiarities and serve, at the same time, to distinguish the disease from pseudoleukemia and other lesions with which it has been confounded. For these purposes the term "Hodgkin's granulomatous lymphoma" appears to be suitable, since it designates the type of tissue in which the disease commences, the initial changes by which it is characterized, and the secondary changes that occur in the course of its development, while it reserves to Hodgkin the recognition that is due him. At all events, it is scarcely justifiable to employ the term "pseudoleukemia" as a synonym for "Hodgkin's disease," since the two

processes, when fully developed, are readily separable and present totally different histological alterations.

2. From the histological features described in the spleen in the case first presented I think it is shown that there is a primary splenic form of Hodgkin's disease, while Cases 2 and 3 serve to emphasize the fact that the abdominal lymph nodes may be the seat of origin.

3. The histogenesis of Hodgkin's disease, both in the lymphatic system proper and in the viscera, appears to be conceived in the formation of lymphomatous foci, while the characteristic granulomatous changes are sequential.

In conclusion I wish to acknowledge my gratitude to Dr. Harrison S. Martland, pathologist to the Newark City Hospital, for the drawing in the case of primary splenic Hodgkin's disease and to Dr. Charles E. Farr for the photograph of the intestine in the case of pseudoleukemia.

7 West Fifteenth Street.

ADDITIONAL REFERENCES

16. Carrington: Tr. Path. Soc., London, 1884, xxxv, 386.
17. Hadden: Tr. Path. Soc. Lond., 1888, xxxiv, 128.
18. Pitt: Tr. Path. Soc., London, 1889, xl, 80.
19. Schlesinger: Ztschr. f. klin. Med., 1897, xxxii, Suppl. Heft, 179.
20. Herrick: Tr. Chic. Path. Soc., 1897-99, iii, 345.
21. Stoerck: Wien. klin. Wchnschr., 1904, xvii, 4.

SPHYGMOGRAPHIC STUDY OF A CASE OF COMPLETE HEART-BLOCK

A CONTRIBUTION TO THE STUDY OF THE ACTION OF STROPHANTHUS ON THE HUMAN HEART*

GEORGE BACHMANN, M.D.
PHILADELPHIA

One of the most interesting of the disturbances of cardiac function is the one known as heart-block, a condition in which the auricular and ventricular rhythms are dissociated and in which a most notable infrequency of the pulse is usually observed. The experimental work of Humblet,[1] Hering,[2] and of Erlanger[3] on the atrioventricular bundle of His and the concomitant observation that heart-block may occur spontaneously in man have so stimulated the study of bradycardia that, within a few years, a relatively large number of cases presenting the phenomenon of auriculoventricular dissociation has been reported. Dissociation of the contractions of auricles and ventricles is most often found in patients suffering from the Adams-Stokes syndrome. There have been, however, a few undoubted cases exhibiting the symptom-complex of permanent bradycardia in association with syncopal or epileptiform attacks, in which the condition of auriculoventricular dissociation could be definitely excluded (Lépine[4]). On the other hand, heart-block, either complete or incomplete, has been found in cases in which there were at no time any of the nervous phenomena which characterize the

---

*From the laboratories of the Jefferson Medical College Hospital.

1. Humblet: Le faisceau inter-auriculo-ventriculaire constitue le lien physiologique entre les oreillettes et les ventricules du cœur du chien. Arch. internat. de physiol., 1904, i, 278; 1906, iii, 330.

2. Hering, H. E.: Ueber die Erregungsleitung zwischen Vorkammer und Kammer des Säugetierherzens. Arch. f. d. ges. Physiol., Bonn, 1905, cvii, 97.

———. Nachweis, dass das His'sche Uebergangsbündel Vorhof und Kammer des Säugetierherzens functionell verbindet. Zweite Mitteilung. Ibid., 1905, cviii, 267.

3. Erlanger, J.: The physiology of heart-block in mammals with especial reference to the causation of Stokes-Adams disease. Jour. Exper. Med., 1905, vii, 676; 1906, viii, 8.

4. Lépine, R.: Sur un cas de syndrome d'Adams-Stokes sans blocage. Semaine méd., 1907, xxvii, 601-603.

Adams-Stokes syndrome (Mackenzie,[5] Joachim,[6] Gerhardt,[7] James,[8] Chauffard,[9] Gibson,[10] Jellinek and Cooper,[11] Bachmann[12]). Heart-block, of a transitory character, may also be observed in digitalis poisoning.

The observations recorded in the present paper were made on the patient presenting the Adams-Stokes symptom-complex whose clinical history will be reported by Dr. Kalteyer later.

The notably infrequent pulse and the presence of relatively frequent faint fluttering pulsations at the root of the neck made one suspect the cause of the bradycardia to be dissociation in the action of auricles and ventricles. The movements of the apex beat, carotid and jugular pulses were accordingly recorded in order to decide this question.

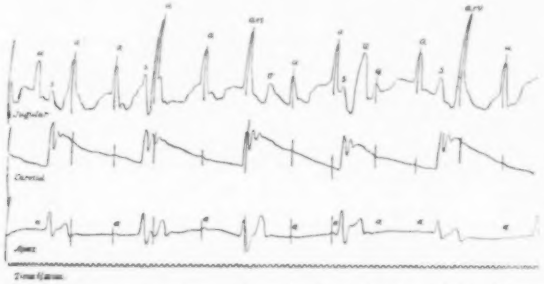


Fig. 1.—Simultaneous tracings of pulsations in the right internal jugular vein, carotid artery and of the apex-beat (Dec. 30, 1908).

Figure 1 is one of the tracings obtained during the first days of the patient's stay in the hospital. This tracing shows that the ventricular contractions were infrequent and regular, and that each of these was

5. Mackenzie, J.: The cause of heart irregularity in influenza. Brit. Med. Jour., 1902, ii, 1411.

6. Joachim, G.: Das Verhalten des linken Vorhofes bei der Störung der Reizleitung. Ztschr. f. klin. Med., 1907, lxiv, 95.

7. Gerhardt, D.: Beitrag zur Lehre vom Pulsus intermittens und von der paroxysmalen Bradycardie. Arch. f. exper. Pathol. u. Pharmakol., 1904, li, 11.

8. James, W. B.: A clinical study of some arrhythmias of the heart. Am. Jour. Med. Sc., 1908, cxxxvi, 469.

9. Chauffard: Bradycardie asystolique. Rev. gén. de. clin. et de thérap., 1907, xxi, 437.

10. Gibson, G. A.: A discussion on some aspects of heart-block. Brit. Med. Jour., 1906, ii, 1113.

11. Jellinek, E. O., and Cooper, C. M.: Report, with comment, of six cases of heart-block, with tracings, and one postmortem examination of the heart. Brit Med. Jour., 1908, i, 796.

12. Bachmann, G.: Complete auriculoventricular dissociation without syncopal or epileptiform attacks. Am. Jour. Med. Sc., 1909, cxxxvii, 342-364.

followed by a carotid pulsation; the auricular contractions (a), as reflected in the jugular pulsations, were from two to three times as frequent as the ventricular contractions. The auricles and ventricles exhibited, therefore, a different rhythm, each rhythm, moreover, bearing no definite relations to the other. In other words, the ventricular contractions were absolutely independent of the auricular contractions, and the notable bradycardia observed in the patient was due to the failure on the part of the auricles to excite the ventricles to contraction. There was, therefore, a complete block to the passage of the excitation wave from the auricles to the ventricles, and the latter were beating by virtue of their own power of rhythmic stimulus-production.

The ventricular and auricular rates of contraction during the first days the patient was under observation are given in Table 1.

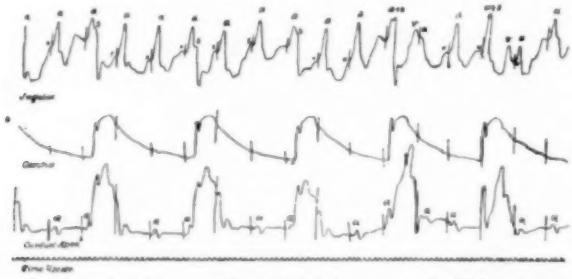


Fig. 2.—Tracing showing a well-marked "sinus wave." This wave, attributed to the contraction of the mouth of the precava, is marked by an X (Dec. 31, 1908).

TABLE 1.

Date	No. of Vs.	Duration in 1/10 sec.	No. of Vs. per. min.	No. of As.	Duration in 1/10 sec.	No. of As. per. min.	As : Vs
Oct. 27, 1908..	13	206	37.86	34	238	85.71	2.26:1
Oct. 28, 1908..	23	411	33.57	53	424	75	2.23:1
Oct. 30, 1908..	19	352	32.38	44	359	73.53	2.27:1
Oct. 30, 1908..	18	345	31.3	43	364	70.87	2.26:1
Oct. 30, 1908..	15	283	31.8	38	313	72.84	2.29:1
Average	—	——	33.38	—	——	75.59	2.26:1

A closer analysis of the tracing (Fig. 1), which may be used as a type, shows in the record of the jugular pulsations a number of positive waves of unequal heights. Those marked *a* are referable to the contractions of the right auricle; those marked *s* are due to the upward projection of the tricuspid valve into the cavity of the auricle at the beginning of ventricular systole. These correspond to the wave usually designated *c*, and in this instance it is often vitiated by the pulsation

of the subclavian artery, owing to the latter's abnormally high position above the clavicle. The third positive wave, *v*, is probably attributable to the relaxation of the papillary muscles and the ascent of the auriculo-ventricular septum at the end of ventricular systole. The height of the auricular waves varies according to the time of occurrence of the auricular contractions, being very high when the auricular contraction

Fig. 3.—Tracing from the right radial artery. There are no abnormal waves on the katacrotic limb of the pulse wave as seen in most of the other tracings obtained from the carotid artery.

takes place during ventricular systole, and very low when the auricular contraction occurs shortly after the beginning of ventricular diastole. This finds its explanation in the ventricular pressure changes occurring during the cardiac cycle. If, when the ventricle is in a state of contraction, the auricle suddenly contracts, the rise of intra-auricular pressure which follows is sufficient to overcome the high intraventricular

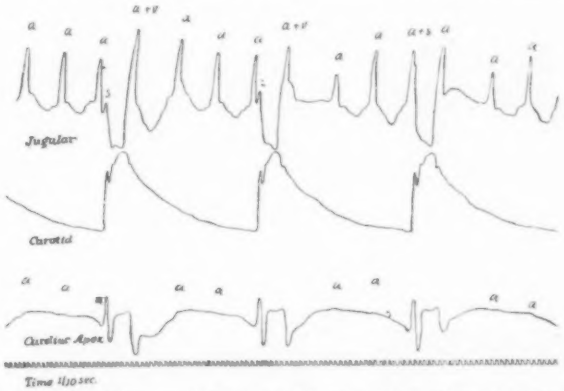


Fig. 4.—Tracing taken on Nov. 19, 1908, at a time when the syncopal and epileptiform attacks had become more frequent and more severe. The apparent 4:1 rhythm is purely accidental.

pressure, and the auricular blood will be forced backward into the large veins, which in consequence will be suddenly and forcibly distended. When the auricular contraction takes place, either at the beginning or toward the end of ventricular systole, the resulting wave is also very high. This high wave is due, in the first instance, to the addition of the *s* to the *a* wave; in the second instance, to a blending of the *v* with

the *a* wave. In either case the resulting compound wave is generally higher than either wave taken separately. A small wave immediately preceding the *a* wave can be seen in most of the tracings illustrating this article. This wave has been observed and described by Erlanger and by Gibson, and has been attributed by them to the contraction of the mouth of the vena cava (sinus contraction); it is more likely to appear when the veins are well filled. This *sinus* wave is especially well de-

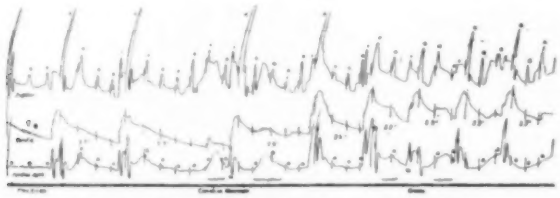


Fig. 5.—Tracing taken during a short attack.

fined in Figure 2, which was taken on a day (Dec. 31, 1908) when the jugular veins were more distended than usual.

The carotid pulse in nearly all the tracings is of the anacrotic type and has the rounded summit typical of the senile pulse. There are faint indications of small waves on the katacrotic limb of the pulse wave outside of those normally found there. They bear a definite relation to the *a* waves of the jugular pulse, and are in all probability due to the

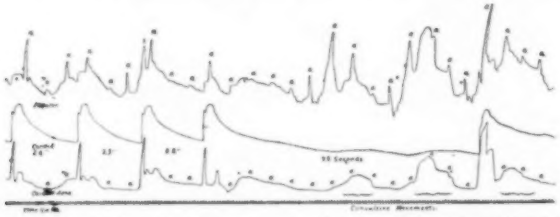


Fig. 6.—Tracing taken during a longer attack. Note the prolonged stoppage in the ventricular contractions and that the convulsive movements do not occur until toward the end of the ventricular silence. The auricles go on beating regularly.

latter. That they are not produced by variations in intraventricular pressure affecting the arterial blood column is shown by the absence of such waves in the radial pulse (Fig. 3). When these waves are intrinsic in the artery they may be demonstrated in the radial pulse, as in Webster's case and in some of Gibson's cases, or in the brachial pulse, as in Erlanger's case.

The record of the apex-beat varies in appearance in the various tracings. This is due, in part, to changes which took place in the tonicity of the heart, the systolic plateau becoming better sustained as the patient improved, but in greater part to changes in the position which the patient assumed while the tracings were taken from day to day. The patient suffered at first from orthopnea and had to be propped up, with the result that the heart receded from the chest wall; as improvement progressed it became possible for the patient to assume the recumbent posture without inconvenience; under such circumstances a better record of the apex-beat was obtained, as shown by the later tracings. The ventricular systole is somewhat prolonged, lasting from 0.4 to 0.5 second. The diastolic period is interrupted by a varying number of small waves which correspond to the *a* waves of the jugular tracing, and have the same significance. The auricular contractions, which, as mentioned above, occur during the ventricular contraction, influence the form of the systolic plateau in that they deform it, usually causing a pronounced indentation or a "crushing" of its summit. This effect of an auricular contraction on the form of the systolic could not serve as a reliable means of identifying an auricular systole, so that a record of the apex-beat alone can not be used for estimating the number of auricular contractions in the cardiac cycle in cases of auriculoventricular dissociation.

From the time of admission (Oct. 26, 1908) until November 10 following, the patient had six attacks of vertigo followed by loss of consciousness. On November 10 the syncopal attacks became more frequent and were accompanied by epileptiform convulsions. A number of tracings were taken on this date, but no syncopal attack occurred during the observation. The analysis of the tracings, however, revealed the interesting fact that, while the auricular frequency had remained practically unchanged, the ventricular frequency had fallen considerably.

TABLE 2.

Date	No. of Vs.	Duration in 1/10 sec.	No. of Vs. per. min.	No. of As.	Duration in 1/10 sec.	No. of As. per. min.	As : Vs
Nov. 10, 1908..	9	269	20.07	31	276	67.5	3.36:1
Nov. 10, 1908..	10	280	21.42	37	281	78.28	3.65:1
Nov. 10, 1908..	9	260	20.76	33	264	75	3.61:1
Nov. 10, 1908..	9	272	19.85	34	280	72.85	3.67:1
Nov. 10, 1908..	9	280	19.28	38	295	77.2	4. :1
Nov. 10, 1908..	8	238	20.16	33	240	82.07	4. :1
Average	—	——	20.25	—	——	75.48	3.72:1

A comparison of Table 2 with the preceding one shows that the ventricular frequency fell from an average of 33.38 per minute to an average of 20.25 per minute. The auricular frequency, as stated above, did

not change, so that the As : Vs ratio became in consequence greater, the average being 3.72 : 1, instead of 2.26 : 1, as in Table 1, while in some individual tracings this ratio reached 4 : 1 (Fig. 4). It seems as if there were some direct relation between the slowing of the ventricular contractions and the increased frequency and severity of the syncopal attacks. Accordingly, this slowing of the ventricles might be regarded as the expression of a general tendency on their part to cease contracting, at least temporarily, and thereby to bring about the various nervous phenomena observed in the Adams-Stokes syndrome, through anemia of the nerve centers. In this case, as in most cases so far reported, it was observed that the syncopal and epileptiform attacks were immediately preceded by a complete disappearance of the pulse for a variable period

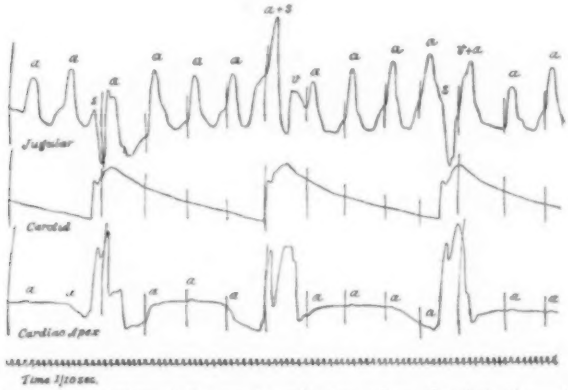


Fig. 7.—Tracing taken 4 hours 30 minutes after the injection of atropin (Nov. 14, 1908).

of time, usually a few seconds (4 to 8). In one instance, however, the pulse disappeared from the wrist for fully four minutes, when the patient became relaxed and was apparently lifeless. Dr. Hull, the interne on duty, raised the foot of the bed and performed artificial respiration. His efforts were rewarded by a return of the patient to consciousness; the pulse-rate rose rapidly to 120 per minute, to return shortly after to its usual low rate. This increased ventricular frequency, at the end of an attack, has been observed in many cases of Adams-Stokes syndrome.

The presence of a complete auriculoventricular dissociation having a permanent character is strongly suggestive of an organic lesion of

the muscle bundle of His.[13] Nevertheless, in order definitely to exclude the possibility of this disorder originating in some disturbance in the innervation of the heart, the atropin test was applied. Dehio was the first to employ atropin as a means of determining the part played by the cardio-inhibitory apparatus in infrequent or in irregular action of the heart. The same observer used the atropin test in a case of Adams-Stokes symptom-complex and found that the drug did not influence the pulse-rate in any notable manner. Since then atropin has been used by a number of investigators in similar cases. The effect of atropin on the heart, under such circumstances, varies with the degree of heart-block present. When the block is complete, atropin causes a more or less marked increase in auricular frequency while the ventricular rate remains practically unchanged; when the block is incomplete, the increase in auricular frequency is accompanied by an increase in ventricular frequency, owing to the circumstance that some of the auricular impulses are able to reach the ventricles and excite these to contraction. The action of atropin in heart-block is explained by the fact, established experimentally by Erlanger and others, that the vagus nerve acts directly on the auricles only (possibly only on the right auricle); the increased ventricular (pulse) rate which normally follows the sus-

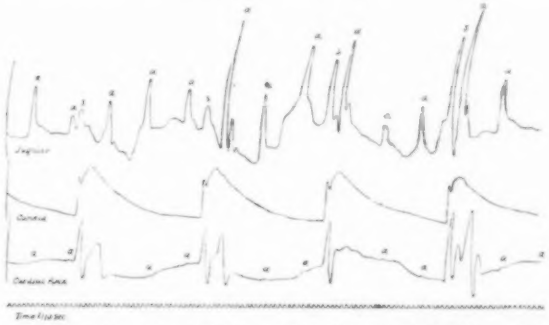


Fig. 8.—Tracing taken immediately before the administration of strophanthus (Nov. 20, 1908).

13. Some doubt has been expressed by Kronecker and Imchanitzky concerning the generally accepted opinion that the muscle bundle of His is the pathway conducting the excitation process from auricles to ventricles; they maintain that ligation and crushing of the bundle of His proper, without including in the ligature any of the adjacent tissues, will not cause any incoordiation between auricular and ventricular action (Arch. internat. de physiol., 1906, iv, July). Paukul, working in Kronecker's laboratory, has recently confirmed the findings of the above named investigators (Ztschr. f. Biol., 1908, li, 178-196.

pension of vagus action is secondary to the increased auricular rate. The presence of a complete block between auricles and ventricles naturally renders the latter absolutely independent of any change in the rate of the former.

The dose of atropin ordinarily recommended for this test is 1/50 grain hypodermically, but owing to the patient's unfavorable condition it was thought safer to administer a smaller dose—viz.: 1/100. The results are given in Table 3.

TABLE 3.—EFFECT OF ATROPIN, 1/100 GRAIN HYPODERMICALLY

Time Injection of atropin.	No. of Vs.	Duration in 1/10 sec.	No. of Vs. per min.	No. of As.	Duration in 1/10 sec.	No. of As. per min.	As:Vs.	Remarks.
Before....	6	175	20.57	24	184	78.26	3.80:1	
Before....	7	202	20.79	28	206	81.55	3.92:1	
Before....	7	202	20.79	26	198	78.78	3.78:1	
After—								
Hr.Min.								Atropin injected.
5.....	7	197	21.32	27	210	77.14	3.61:1	
8.....	7	192	21.87	26	205	76.09	3.48:1	
12.....	7	199	21.10	26	214	72.89	3.45:1	
18.....	6	222	16.21	33	230	86.09	5.31:1	Vs. irregular.
23.....	8	224	21.42	30	235	76.59	3.57:1	Vs. regular.
28.....	9	259	20.84	33	262	75.57	3.62:1	Vs. regular.
33.....	9	277	19.48	37	280	79.28	4.12:1	Vs. irregular.
37.....	9	280	19.28	39	289	80.96	4.2 :1	Vs. regular.
43.....	9	273	19.78	37	285	77.89	3.94:1	Fig. 5.
48.....	8	248	20.	37	259	85.71	4.28:1	Vs. regular.
58.....10		246	24.39	37	250	88.8	3.64:1	Syncopal attack.
1.14.....	8	257	18.67	39	275	85.1	4.55:1	Vs. stopped 4.8 sec. Fig. 6.
1.19.....	8	274	17.52	44	291	90.72	5.17:1	Syncopal attack.
1.25.....11		295	22.37	43	280	92.14	4.11:1	Vs. stopped 4.9 sec. Vs. irregular.
1.31.....	9	291	18.55	52	312	100	5.39:1	Vs. regular.
1.40.....	7	211	19.9	36	257	84.04	4.22:1	Syncopal attack. Vs. stopped twice, each 4.9 sec.
1.46.....	7	216	19.44	37	230	96.52	4.96:1	Vs. regular.
1.53.....	6	184	29.34	35	218	96.33	3.28:1	Vs. regular.
2	7	211	19.9	38	234	97.43	4.89:1	Vs. regular.
4.30.....	9	256	21.09	40	266	90.22	4.27:1	Vs. regular.
4.35.....	8	232	20.69	32	241	79.66	3.85:1	Vs. regular.
4.40.....	8	234	20.51	34	246	82.92	4.04:1	Vs. regular.
4.45.....	8	232	20.69	36	240	90.	4.35:1	Vs. regular.
4.50.....	7	219	19.17	30	229	78.6	4.1 :1	Vs. regular.

The above analysis of the tracings shows the usual outcome of the atropin test in cases of complete heart-block—namely, acceleration of the auricles—the ventricular rate remaining unaffected. But definite conclusions from the ventricular action can not be drawn in this instance because of its irregularity during the greater part of the test. Several typical attacks occurred while the tracings were being taken. The dependence of the convulsive seizures on the cessation of the ventricular contractions is well illustrated in tracings Figures 5 and 6, where the

time of occurrence of the convulsive movements is plainly shown. It will be seen also that complete stoppage of ventricular action may occur suddenly without the preliminary gradual slowing generally observed (Fig. 6). Tracing Figure 5 demonstrates the increased ventricular rate which follows an attack. It is a noteworthy fact that nearly all of the instances of ventricular stoppage I was able to record during the observation lasted 4.9 seconds and that the prolonged stoppage seen in Figure 6 is a multiple of this (9.8 seconds). The auricular contractions, under the influence of atropin, remained perfectly regular throughout the test with the exception noted below. The increase in rate was but slight and occurred late—much later than has been observed heretofore. It is probable that the smallness of the dose of atropin employed,

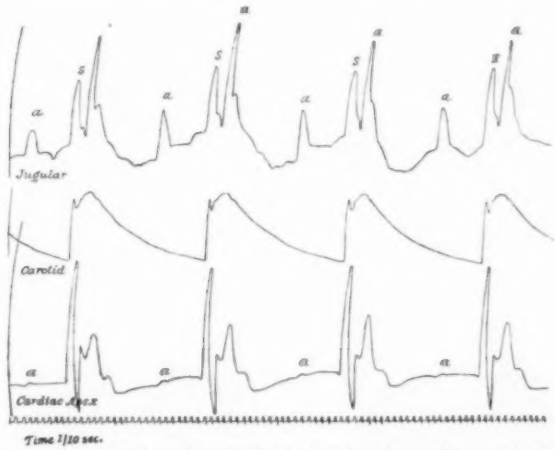


Fig. 9.—Tracing showing the effect of strophanthus. The auricular contractions have decreased, the ventricular contractions have increased in frequency (Nov. 23, 1908).

as well as the sluggish state of the patient's circulation, are the factors responsible for this slight and slow response. There does not seem to be any relation between the stoppage of the ventricles which precedes an attack and the frequency of the auricular contractions. Erlanger states that in the case he studied the slowing of the ventricles was synchronous with a sudden acceleration of the auricles. I was unable to confirm this observation in the case under discussion. The auricular rate, it is true, increased under the influence of atropin; this increase, however, was not a sudden but a gradual one, and the observation made by Erlanger that atropin will not call forth an attack is attributed by him

to this circumstance. The only thing of note in this connection is a slight and momentary auricular arrhythmia which took place during a mild attack (Fig. 5). This is the only instance in which this was observed and may have been, therefore, nothing but a coincidence. The complete dissociation of the action of auricles and ventricles, together with the results of the atropin test, indicate that the break in the conducting path between auricles and ventricles is complete and constitutes strong presumptive evidence of an organic lesion implicating the bundle of His to a marked extent. An opportunity is thereby made available for the study of drugs used in cardiac therapeutics, about whose mode of action there may still be some doubt. Such a drug is strophanthus. Germain Sée and Gley, Delseaux[14] and other pharmacologists are of the opinion that strophanthus does not modify the cardiac rhythm through any action on the medulla or on the cardiac nerves. On the

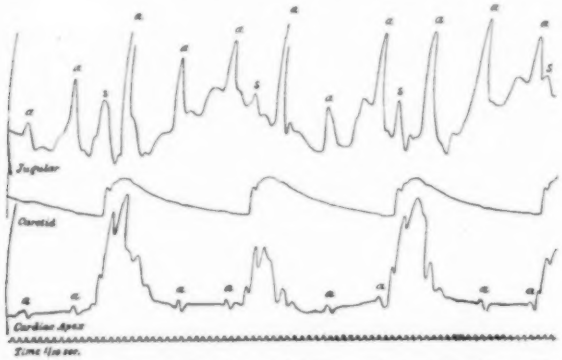


Fig. 10.—Tracing taken after the withdrawal of strophanthus. Note the return of auricular contractions to their former rate. The action of the entire heart has increased in strength as shown by the increased height of the auricular and ventricular contractions (Dec. 29, 1908).

other hand, Kochmann[15] observed that, after section of both vagi, strophanthin (Merck) did no longer diminish the rate of the heart-beat. Liagre[16] was able to fully confirm these latter findings with both the tincture of strophanthus and strophanthin. He found, also, that these preparations will fail to slow the heart's action when the vagi have had their conductivity suspended by means of atropin. He demon-

14. Sée, Germain, and Gley and Delseaux (quoted by Liagre): Jour. de physiol. et de path. gén., 1906, viii, 988).

15. Kochmann: Beitrag sur Wirkung einiger Körper der Digitalisgruppe auf den N. Vagus. Arch. internat. de pharmocod., 1906, xvi, 221.

16. Liagre, C.: Action de la teinture de strophantus et de la strophantine sur le rhythme du cœur. Jour. de physiol. et de path. gén., 1906, viii, 988.

strated, furthermore, that strophanthus, or its alkaloid, does not produce any bradycardia in the perfused and isolated heart, but that, on the contrary, a noticeable tachycardia ensues which, if the dose be too large, is complicated by arrhythmia.

In a previous communication[12] I showed that strophanthus given in medicinal doses, in a case of complete heart-block, decreases the auricular rate, while the ventricular rate remains practically constant. The action of the drug was also studied in this case. Five minims of the tincture of strophanthus (U. S. P.) was given three times a day from November 21 till November 25, on which date the dose was increased to ten minims. The administration of the drug was continued at this dose till Dec. 7, 1908, when it was withdrawn altogether. Tracings were taken just before the administration of strophanthus and then afterward, sufficiently often to determine the reaction of the heart toward the drug; the observations were continued after its withdrawal. The results are presented in Table 4, and are also graphically represented in a chart (Fig. 12).

TABLE 4.—EFFECT OF STROPHANTHUS

Date.	No. of Vs.	Duration in 1/10 sec.	No. of Vs. per min.	No. of As.	Duration in 1/10 sec.	No. of As. per min.	As:Vs.	Remarks.
11/20, '08..	8	207	23.18	25	204	73.52	3.15:1	Before.
	8	203	23.64	26	219	71.23	3.01:1	
	8	201	23.88	26	214	72.89	3.05:1	
	9	238	23.68	28	235	71.48	3.15:1	
11/21, '08..	—	—	—	—	—	—	—	Strophanthus m.v. t.i.d.
11/22, '08..	26	681	22.9	78	729	64.19	2.8 :1	Strophanthus m.v t.i.d.
11/23, '08..	55	1208	27.31	116	1271	54.76	2. :1	Strophanthus m.v t.i.d.
11/25, '08..	55	1477	22.34	180	1535	70.35	3.14:1	Strophanthus m.x t.i.d.
11/26, '08..	31	592	31.41	64	600	64.	2.03:1	Strophanthus m.x t.i.d.
11/27, '08..	22	399	33.08	46	417	66.18	2.00:1	Strophanthus m.x t.i.d.
11/28, '08..	48	904	31.85	88	938	56.29	1.45:1	Strophanthus m.x t.i.d.
11/29, '08..	30	619	29.07	61	636	57.54	2.2 :1	Strophanthus m.x t.i.d.
11/30, '08..	34	728	28.02	74	753	58.96	2.1 :1	Strophanthus m.x t.i.d.
12/2, '08..	25	512	29.29	56	521	64.49	1.98:1	Strophanthus m.x t.i.d.
12/5, '08..	38	794	28.71	90	807	66.91	2.33:1	Strophanthus m.x t.i.d.
12/7, '08..	40	836	28.7	93	879	63.48	2.21:1	Strophanthus stopped.
12/9, '08..	30	636	28.3	81	701	69.32	2.44:1	
12/11, '08..	30	664	27.1	78	680	68.8	2.53:1	
12/13, '08..	36	774	27.9	97	817	71.23	2.55:1	
12/15, '08..	58	1234	28.2	175	1308	80.27	2.84:1	
12/17, '08..	52	1058	29.53	138	1113	74.39	2.51:1	
12/19, '08..	48	1016	28.34	128	1070	71.77	2.53:1	
12/20, '08..	34	692	29.47	100	720	83.33	2.82:1	
								Gone home for Christmas.
12/27, '08..	44	989	26.69	137	1073	76.6	2.86:1	
12/29, '08..	42	887	28.41	131	968	81.2	2.85:1	
12/31, '08..	52	1032	30.23	162	1102	88.2	2.91:1	
1/2, '09..	52	1151	27.1	155	1228	75.73	2.8 :1	
1/4, '09..	43	910	28.35	135	960	84.37	2.97:1	
1/6, '09..	45	963	28.03	151	1020	88.88	3.17:1	Six groups of 4:1 ratio.
1/8, '09..	54	1123	28.85	156	1157	80.9	2.8 :1	
1/10, '09..	42	926	27.21	135	992	81.65	3. :1	

The most striking effect of the action of strophanthus on the heart's action is seen in the notable decrease in the frequency of the auricular contractions. It is to be noted that no such effect is exerted upon the ventricular contractions; on the contrary, these are conspicuously increased in rate. In this way is brought about an approximation toward normal heart action, as shown by the decrease in the As : Vs ratio. These findings are a confirmation of the statement I made in another place, that strophanthus slows the heart by stimulating the vagus nerve. They also confirm the animal experiments of Kochmann and of Liagre and show the propriety of their application to the human heart. The ventricles in this case exhibit the tendency to acceleration manifested in the tachycardia of the isolated and perfused heart when it is subjected to the action of strophanthus. Von Tabora[17] made some experiments on the mammalian heart which may be of interest in this

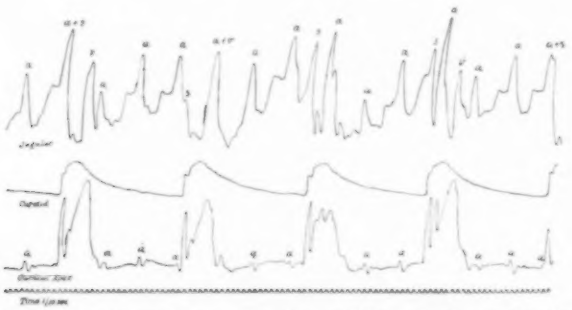


Fig. 11.—Tracing taken later after the withdrawal of strophanthus. The auricular frequency continues to increase. The improved cardiac condition persists (Jan. 6, 1909).

connection. After crushing the bundle of His, thereby producing a complete and permanent auriculoventricular dissociation, this investigator injected digitalin intravenously; the results which he obtained were a doubling of the ventricular rate and a gradual decrease in the auricular rate going on to complete arrest. Thus it will be observed that there exists a certain parallelism in the mode of action of strophanthus and digitalis (digitalin) in bringing about a decrease in the frequency of the heart beat.

17. Von Tabora, D.: Ueber die experimentelle Erzeugung von Kammersystolenausfall und Dissociation durch Digitalis. Ztschr. f. exper. Path. u. Therap., 1906, iii, 549.

That the slowing of the auricles was not fortuitous is shown by the fact that, following the complete withdrawal of the drug, their rate gradually increased until it reached and went beyond the figure which it had before the test. The tonic action of the drug on the ventricles persisted, so that their frequency remained a little higher than immediately before the test.

The improvement of the circulation under the influence of strophanthus had a most remarkable result. The syncopal and epileptiform seizures which had been increasing in frequency and severity gradually became less frequent and in a short time disappeared, not to return

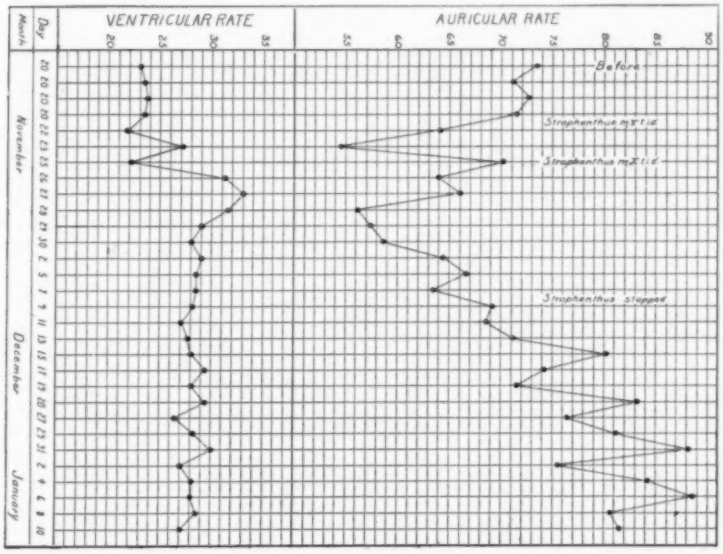


Fig. 12.—Chart based on Table 4, showing the effect of strophanthus on the auricular and ventricular rates. Apparently, the auricles either escape from vagus stimulation or the vagus ultimately fails to respond to the prolonged action of the drug.

again, even after the withdrawal of the drug. The patient ultimately felt so well that he left the hospital.

Jagic[18] has reported a case of Adams-Stokes syndrome in which a temporary improvement followed the administration of small doses of digitalis (0.05 gm. a day). He supposes that this result was an effect

18. Jagic, N.: Ein Beitrag zur Kasuistik des Adams-Stokes'schen Symptomenkomplexes. Ztschr. f. klin., Med., 1908, lxvi.

of the small dose of digitalis used, which, he thinks, could hardly have stimulated the vagus, but could, nevertheless, have acted directly on the heart muscle.[19] He states that digitalis in larger doses may do harm by further depressing conduction through vagus stimulation; but, as his case was in all probability one of complete heart-block, and as Erlanger's experiments, as well as the atropin and strophanthus tests, indicate that the vagus influences the auricle only, Jagic's fears do not appear well founded. That vagus stimulation, in cases of complete block, is not incompatible with decided improvement in ventricular action is shown in the study of the effect of strophanthus herein reported. The result might be different in cases of incomplete heart-block, for in this condition some of the auricular impulses pass over to the ventricles, and usually these are still dependent for their contraction on the arrival of the auricular impulses. A slowing of the auricles, through the action of digitalis or strophanthus on the vagus, would inevitably be followed by a decrease in the frequency of the ventricular contractions. Digitalis might, moreover, further depress the conductivity of the auriculoventricular bundle. The combination of these two effects would naturally aggravate the condition. Such a result is apparently not to be feared in cases of complete heart-block.

I wish here to express my indebtedness to Professor J. C. Wilson for the privilege of studying the case.

19. The article does not contain any tracings, nor is there any mention of any having been taken.

EFFECTS OF THE ADMINISTRATION OR THE WITHHOLDING OF IODIN-CONTAINING COMPOUNDS IN NORMAL, COLLOID OR ACTIVELY HYPERPLASTIC (PARENCHYMATOUS) THYROIDS OF DOGS

SOME EXPERIMENTS ON (CONGENITAL) PRENATAL THYROID HYPERPLASIA IN DOGS; REMARKS ON THE CLINICAL MANIFESTATIONS ASSOCIATED WITH MARKED THYROID HYPERPLASIA *

DAVID MARINE, M.D., AND C. H. LENHART, M.D.
CLEVELAND, OHIO

The observations and experiments here recorded have been made on dogs, and include three with normal, eight with colloid and seventeen with actively hyperplastic glands, as ascertained by the first specimen of thyroid removed. The plan followed has been to remove a control portion of the thyroid from each dog for histologic diagnosis and iodin determination, and at intervals to remove other portions for comparison.

Our experiments may be divided into two groups: (1) those in which iodin was administered and (2) those in which no iodin was administered, except what was contained in a liberal diet of cooked meat, bread, sodium chlorid, milk and water. The food being the same in each group, no other remarks are necessary, except that dogs normally store some iodin from such a diet. These two groups have been tabulated, and in presenting Tables 1 and 2 we have arranged the cases according to the anatomic groups represented, as ascertained by the histologic diagnosis of the first specimen of thyroid removed. Thus normal and colloid glands are placed first; then follow in order the several degrees of hyperplasia.

We shall discuss the cases according to the groups represented.

1. *Normal Glands.*—Of the three subjects (A-123, A-26, A-27), only one (A-26) was given iodin directly. In this case the iodin was distinctly but not markedly increased in the remaining lobe. This lobe also increased in size, but remained normal in structure. The other two subjects (A-123 and A-27) showed hyperplasia of the remaining lobes. These three cases show that iodin does have a preventive effect on the

*From the Laboratories of Experimental Medicine and Pharmacology of Western Reserve University.

hyperplasia and also that iodin is increased even in normal glands, though slightly. This is what is expected when one recalls the normally wide variations in the iodin contents of normal glands from all animals.[1] The other point of importance, namely, that glands may grow in size and yet never show any deviation from normal structure, is of considerable interest, in that it furnishes additional proof that hyperplasia, however slight, is no part of the normal growth of normal glands, but must be the evidence of some abnormal factor or stimulus. Further, it shows that the administration of iodin will not prevent the normal growth of a normal gland. Lastly, when the three cases are taken together, it is seen that the amount of thyroid removed is of secondary importance to the iodin content in determining the occurrence of hyperplasia, although iodin does not seem to prevent hyperplasia after a certain maximum of thyroid is removed, just as it does not prevent the normal growth of pups' thyroids. It will be noted that all three dogs were young. This, as Horsley[2] and all subsequent investigators have shown, is very important, since the needs for the gland's activities are greater in youth. The symptoms following the removal of the thyroid are also greater, and compensatory hyperplasia occurs more constantly and more rapidly the younger the animals are.

Colloid Glands.—There were three cases (A-51, A-120, A-118) in which iodin was given and five cases (A-63, A-95, A-104, A-106, A-122) in which it was not given. In the five cases in which iodin was not given there was a gradual lessening of iodin in the succeeding portions removed, just as in the normal glands. This is in sharp contrast with the hyperplasias, all of which will be seen to have gained slightly in iodin. It suggests that the ability of normal or colloid glands to store iodin from the food is much less than that of actively hyperplastic glands. While in general the iodin contents of colloid glands per gram are less than those of normal glands per gram, this is not necessarily true. The three glands in which iodin was administred show a marked increase in the thyroid iodin, though, as will be seen, it is not as great as that which occurs in the active hyperplasias, thus agreeing with the normal glands in this respect. In two of the cases, A-104 and A-106, secondary (i. e., glands undergoing active hyperplasia for the second time) compensatory hyperplasia occurred, but only after the iodin had been greatly reduced. This also is in harmony with what nor-

1. Marine and Lenhart: Further observations on the relation of iodin to the structure of the thyroid gland in the sheep, dog, hog and ox. THE ARCHIVES INT. MED., 1909, iii, 66.

2. Horsley: Brit. Med. Jour., 1892, i, 215.

mally occurs in the spontaneous secondary hyperplasias. In the case of colloid glands, just as was shown for normal glands, the amount of gland removed does not seem to be so important as is the iodin content in starting the hyperplasia and, also just as in the normal glands, there is a level below which iodin will not protect against secondary hyperplasia. All the evidence taken together indicates that colloid glands behave exactly as normal glands when subjected to the same experiments, or, in other words, that colloid glands parallel normal glands.

Hyperplasias.—Discussing the six cases in which no iodin was directly administered, it will be seen that they represent degrees of hyperplasia from *early* to *moderate*. They all show an increase of iodin in the successive portions removed. This is in sharp contrast with the normal and colloid glands, which under the same conditions of food and experiment did *not* show increases of iodin. Associated with this slight gradual increase in iodin, there is a slow return toward colloid glands. This slow return toward the colloid condition should be contrasted with the rapid return to the colloid condition in those cases given iodin directly.

Taking up the cases of hyperplasia in which iodin was administered, there were eleven, ranging from *normal early* to *marked* glandular hyperplasia. In all these cases very marked and very rapid increases in the iodin contents are shown. Taking the whole series, the general impression is that iodin is stored more rapidly in the cases with marked hyperplasia. This is very evident when colloids or normals are contrasted with the hyperplasias. The form of administration of iodin appears to be of less importance than the degree of hyperplasia in determining the rapidity with which iodin is taken up by the thyroid. The amount of iodin taken up obviously must depend on the quantity administered, the degree of hyperplasia and the extent of the epithelial surface. The rapidity of the involution (reversion) process in subjects given iodin may be judged from A-119 in which noticeable histologic differences were present in five days. This is about the average time required, though we have seen it in three days. The average time required to induce complete involution (reversion) may also be ascertained from this case, in which in 26 days the entire series of changes from marked glandular hyperplasia back to pure colloid gland occurred. How much this may be modified by different methods of administration and different preparations of iodin is yet to be ascertained. Our data indicate that these will be found to be of minor general pharmacologic importance, though probably of great therapeutic importance. Desiccated thyroid preparations appear to have no advantage over the inorganic

Case No.	Sex.	Age.	Weight. Kg.	Day, Month, Year of Operation	Part Removed.	Weight of Thyroid Removed, gm.	Color.	Consistency.	Visible Colloid.	Histologic Diagnosis.
A-26a	F.	3 mos	2.4	15, 2, '07.	R. lobe	0.24	Reddish, transl.	Firm	Normal.	Normal.
A-26b	F.	4½ mos.	4.0	2, 4, '07.	L. lobe	0.305	Yellow, transl.	Firm.	Normal.	Normal.
A-51a	M.	Middle	3.2	29, 3, '07.	L. lobe	22.1	Reddish, transl.	Moderate.	Reduc'd.	Colloid
A-51b	M.	Middle	3.0	4, 4, '07.	R. lobe	23.1	Reddish, transl.	Moderate.	Normal.	Colloid
A-120a	M.	7 mos	3.6	15, 4, '08.	L. lobe	1.7	Yellow, transl.	Firm.	Normal.	Colloid
A-120b	M.	7½ mos.	3.2	2, 5, '08.	R. lobe	1.1	Yellow, transl.	Firm.	Normal.	Colloid
A-118a	M.	3 yrs	9.0	25, 3, '08.	Part of l. lobe.	2.7	Yellow, transl.	Firm.	Normal.	Colloid
A-118b	M.	3 yrs	9.0	30, 3, '08.	Part of l. lobe.	6.5	Yellow, transl.	Firm.	Normal.	Colloid
A-118c	M.	3 yrs	?	4, 4, '08.	Part of l. lobe.	6.0	Yellow, transl.	Firm.	Normal.	Colloid
A-118d	M.	3 yrs	?	10, 4, '08.	Part of r. lobe.	8.25	Yellow, transl.	Firm.	Normal.	Colloid
A-118e	M.	3 yrs	?	15, 4, '08.	Part of r. lobe.	7.3	Yellow, transl.	Firm.	Normal.	Colloid
A-118f	M.	3 yrs	?	6, 5, '08.	Part of r. lobe.	3.3	Reddish, transl.	Moderate.	Visible.	Colloid
A-118g	M.	3 yrs	?	8, 5, '08.	Part of r. lobe.	3.25	Reddish, transl.	Moderate.	Visible.	Colloid early.
A-17a	F.	Middle	5.4	22, 1, '07.	R. lobe	0.7	Gray, transl.	Firm.	Normal.	Normal early.
A-17b	F.	Middle	5.0	15, 3, '07.	L. lobe	0.65	Clear, transl.	Firm.	Normal.	Colloid
A-18a	F.	Middle	5.4	22, 1, '07.	L. lobe	7.5	Grayish, opaque.	Soft.	None.	Mod. gland. hyperplasia.
A-18b	F.	Middle	3.18	11, 2, '07.	R. lobe	4.75	Yellow, transl.	Firm.	Normal.	Colloid
A-73a	M.	Young	8.6	25, 4, '07.	L. lobe	2.6	Reddish, opaque.	Moderate.	None.	Moderate gland. hyperplasia.
A-73b	M.	Young	7.1	4, 5, '07.	R. lobe	2.1	Reddish, transl.	Firm.	Reduc'd.	Colloid. early gland.
A-16a	M.	Old	5.0	22, 1, '07.	L. lobe	4.15	Grayish, opaque.	Soft.	None.	Mod. marked gland. hyperp.
A-16b	M.	Old	3.2	20, 2, '07.	R. lobe	2.7	Yellow, transl.	Firm.	Normal.	Colloid
A-52a	F.	Pup.	2.7	29, 3, '07.	R. lobe	3.6	Grayish, opaque.	Soft.	None.	Mod. marked gland.
A-52b	F.	Pup.	2.8	22, 4, '07.	L. lobe	2.0	Clear, transl.	Firm.	Normal.	Colloid
A-55a	M.	Pup.	7.27	1, 4, '06.	L. lobe	72.0	Opaque.	Soft.	None.	Mod. marked gland. hyperp.
A-55b	M.	Pup.	6.36	8, 4, '09.	R. lobe	57.2	Gray-red, opaque.	Soft.	None.	Moderate gland. hyperplasia.
A-125a	M.	1 yr	6.8	9, 5, '08.	Part of l. lobe.	5.8	Grayish, opaque.	Soft.	None.	Marked gland. hyperplasia.
A-125b	M.	1 yr	6.8	18, 5, '08.	Rem. of l. lobe. R. lobe	93.0 95.0	Grayish, opaque.	Soft.	None.	Moderate marked gland. hyperplasia.
A-114a	F.	8 mos	5.9	19, 2, '09.	Part of l. lobe.	11.6	Grayish-red, opaque.	Soft.	None.	Marked gland. hyperplasia.
A-114a²	F.	8 mos	5.9	19, 2, '08.	Accessory thyroid.	5.0	Grayish-red, opaque.	Soft.	None.	Marked gland. hyperplasia.
A-114b	F.	8 mos	5.0	24, 2, '08.	L. lobe	27.2	Grayish-red, opaque.	Soft.	None.	Mod. marked gland. hyperplasia.
A-114c	F.	8 mos	4.2	26, 2, '08.	R. lobe entire.	23.25	Yellowish, opaque.	Soft.	Visible.	Colloid, mod. gland. hyperp.

WHICH IODIN WAS GIVEN.

Iodin, per gm., Dried.	Iodin, per gm., Moist.	Amount, Form and Duration of Iodid Administration.	Complicating Factors During Experiment.	Remarks.
2.300	0.380	.....	None.	
3.467	0.705	1 c.c. sat. alc. sol. iodid from 2, 21 to 3, 8, '07.	None.....	Chloroformed to death 4, 2, '07.
0.707	0.138	.....	None.	
0.969	0.245	6 5-gr. tablets desiccated thyroid from 3, 29 to 4, 3, '07.	Pneumonia	Death on 5th day of pneumonia.
2.353	0.400	Distemper and chorea on admission.*		
4.480	1.195	Given 70 gtt. syrup of ferr. iodid from Apr. 16 to May 2.	.....	No apparent improvement in distemper and chorea; chloformed to death 5, 2, '08.
0.721	0.186	.....	None.	
1.000	0.237	Given 7.5 gm. of desiccated thyroid containing 1.092 mg. per gm. dried.	None.	
0.477	0.106*	7.5 gm. desiccated thyroid iodid assign'd as above since last opr.	Slight wound infection; $HgCl_2$ dressing.	Iodin determination uncertain owing to presence of mercury.*
1.815	0.487	120 gtt. syr. ferr. iodid since last operation.	Infection cleared up.	
1.146	0.227	120 gtt. syr. ferr. iodid since last operation.	None.	
0.893	0.171	160 gtt. syr. ferr. iodid from 4, 16, to 5, 1.	None.	
0.126	0.026	No iodid since last operation.	Tetany.....	Died 2 days after last operation of tetany.
*	.....	.....	None.....	Iodin not determined — accident — bitch pregnant.*
4.615	1.093	200 mg. iodid given from 1, 26 to 2, 7, '07.	None.....	Killed with chloroform 3, 15, '07.
0.261	0.056	.....	None.	
4.184	1.265	Fed 545 gms. fresh sheep's thyroid from Jan. 25 to Feb. 3.	Emaciation; diarrhea.	Dog died after great loss of weight, associated with serious diarrhea.
0.420	0.071	.....	Canine chorea; "distemper."	
*	.....	5 gtt. sat. alc. iodin from 4, 26 to 4, 30.	Acute distemper..	No iodin determination; specimen lost.
0.086	0.014	.....	None.	
1.739	0.393	Fed 65 5-gr. tablets in 28 days following 1st operation.	Emaciation.....	Killed with chloroform 2, 20, '07; great loss of weight; slight diarrhea.
0.413	0.057	.....	None.	
3.196	0.815	15 gtt. sat. alc. sol. iodin from 4, 1 to 4, 11.	None.....	Killed with chloroform.
0.054	0.008	.....	None.	
1.399	0.292	7 gtt. sat. alc. sol. of iodin since April 2.	Pulmonary embolism.	Dog died suddenly night of April 8, and autopsy showed the pulmonary artery plugged with an embolus.
0.077	0.016	.....	None.	
2.107	0.453	Wound packed 6 times with iodoform gauze.	Wound infection..	Died suddenly May 18, owing to wound being torn open by another dog in a fight.*
0.000	0.000	.....	None.....	Dog was emaciated, pulse 180, heart action shook entire body, slight diarrhea.
0.000	0.000	.....	None.	
1.123	0.243	120 gtt. syr. ferr. iodid fed from 2, 19 to 2, 24.	Slight wound infection.	
1.480	0.352	40 gtt. syr. ferr. iodin in 2 days.	Fatal hemorrhage.	Hemorrhage due to infected silk ligature.

TABLE 1.—EXPERIMENTS IN

Case No.	Sex.	Age.	Weight. Kg.	Day, Month, Year of Operating.	Part Removed.	Weight of Thyroid Removed gm.	Color.	Consistency.	Visible Colloid.	Histologic Diagnosis.
A-116a...	F.	7 mos....	6.5	13, 3, '08..	R. lobe....	6.5	Grayish, opaque.	Soft.....	None.....	Marked gland. hyperplasia.
A-116b...	F.	7 mos....	6.0	17, 3, '08..	R. lobe....	11.6	Grayish, opaque.	Soft.....	Visible...	Colloid mod. marked gland. hyperplasia.
A-116c...	F.	7 mos....	5.5	21, 3, '08..	R. lobe....	27.6	Yellowish opaque.	Firm.....	Visible...	Colloid mod. marked gland. hyperplasia.
A-116d...	F.	7 mos....	5.5	24, 3, '08..	L. lobe....	43.5	Yellowish, opaque.	Firm.....	Visible...	Colloid early gland. hyperplasia.
A-117a...	M.	2 yrs.....	6.9	21, 3, '08..	R. lobe....	4.2	Gray-red, opaque.	Soft.....	None. ...	Marked gland. hyperplasia.
A-117b...	M.	2 yrs.....	6.6	25, 3, '08.	L. lobe } R. lobe } ..	67.10	Yellowish, opaque.	Soft.....	Just visible.	Colloid mod. marked.
A-119a...	M.	8 mos....	8.4	10, 4, '08..	L. lobe....	9.82	Reddish, opaque.	Soft.....	None.....	Marked gland. hyperplasia.
A-119b...	M.	8 mos....	8.2	15, 4, ,08..	L. lobe....	20.5	Yellowish-red, opaque.	Soft.....	Just visible.	Colloid mod. marked gland.
A-119c...	M.	8 mos....	8.0	22, 4, '08..	R. lobe....	1.5	Yellowish, opaque.	Moderate..	Visible...	Colloid mod. gland.
A-119d...	M.	8 mos....	10.0	28, 4, '08..	R. lobe....	7.2	Yellowish, transl.	Firm.....	Normal..	Colloid early gland.
A-119e...	M.	9 mos....	10.5	6, 5, '08...	R. lobe....	6.5	Yellow, transl.	Firm.....	Normal..	Colloid.....
A-119f....	M.	10 mos...	11.9	15, 6, '08..	Remaind'r of lobes.	1.3	Yellow, transl.	Firm.....	Normal..	Colloid.....

salts of iodin, or over pure iodin, in inducing these histologic changes. If anything, the pure iodin is taken up more rapidly. Going back to the cases in which iodin was not administered, it will be seen that in sharp contrast with A-119, in which complete involution (reversion) occurred in twenty-six days, A-121 did not reach complete involution (reversion) for sixty-six days.

FORMS, MODE OF ADMINISTRATION AND AMOUNTS OF IODIN ADMINISTERED

We have employed iodoform, fresh sheep's thyroids, desiccated sheep's thyroid, pure iodin, ferrous iodid, all of which forms are followed by the storage of iodin in the glands, whether normals, colloids or hyperplasias. The resulting histologic effect in all is the same, viz.: the return to the colloid or quiescent condition.

As to the mode of administration: It is taken up by the thyroid when "painted" on the skin, given by mouth or injected hypodermically. On this point, however, we do not possess sufficient data to differentiate specifically between the several modes of administration other than that pure iodin apparently is taken up most rapidly.

WHICH IODIN WAS GIVEN—Continued.

Iodid, per gm., Dried.	Iodid, per gm., Moist.	Amount, Form and Duration of Iodid Administration.	Complicating Factors During Experiment.	Remarks.
0.015	0.003	No iodin administered prior to first operation.	None.....	Rhachitic, anemic and somewhat emaciated, with forcible action and pulse 160; eyes weeping and stools soft.
1.000	0.188	120 gtt. syr. ferr. iodid in 4 days since first operation.	Slight wound infection.	
2.153	0.477	120 gtt. syr. ferr. iodid in 4 days since 2d operation.	Slight wound infection.	
2.691	0.693	80 gtt. syr. ferr. iodid in 3 days.	Fatal hemorrhage.	Hemorrhage due to infected ligature sloughing off a large vein; thymus atrophic; spleen and lymph gland enlarged.
0.065	0.014	No iodin given prior to 1st operation.	None.	
2.384	0.540	120 gtt. syr. ferr. iodid given in 4 days since 1st operation.	Over anesthetized.	Ineffectual efforts at resuscitation.
0.200	0.040	No iodin given prior to 1st operation.	None.....	Anemic, but fat deposits normal.
2.861	0.553	120 gtt. syr. ferr. iodid in 5 days since first operation	None.	
4.078	0.860	300 gtt. syr. ferr. iodid in 7 dys. since 2d ope.	None.	
3.353	0.749	No iodin given since last operation.	None.....	Dog gaining weight rapidly
3.522	0.894	No iodin given.....	None.	
2.770	0.554	No iodin given.....	Killed by negligent anesthetist.	An attempt was made June 1, but no thyroid found in a hasty exam. Dog killed June 15 by negligence after operation was completed.

Coming to the amounts of iodin administered, one of the most striking things brought out is that of the minute amounts (minute in contrast with what we had generally seen recommended in the treatment of goiter) necessary to induce thyroid changes. It appears that the more marked the hyperplasia the greater is the amount of iodin taken up, since in normal dogs one can give very large amounts of iodin without inducing any systemic effect or raising the iodin content of the glands any more than much smaller doses do in actively hyperplastic glands. It may be well to refer to the systemic effects produced by iodin as we have seen them.

In the first place, reference to Tables 1 and 2 will show that in normal or colloid glands there is either little change in body weight or there is about the same change whether iodin was administered or not. This is not true of the subjects with hyperplasia. All such subjects when fed iodin lost weight rapidly for a time (one to two weeks), then started to gain, while in those not fed iodin a loss of weight was not observed. We have made some specific experiments regarding the loss of weight. Thus we took three markedly goitrous pups of the same litter, aged six

TABLE 2.—EXPERIMENTS IN WHICH

Case No.	Sex.	Age.	Weight.	Day, Month, Year of Operation	Part Removed.	Weight of Gland Removed.	Color.	Consistency.	Colloid.
A-27a	F.	3 mos.	1.85	15, 2, '07.	R. lobe	0.15	Reddish, transl.	Firm	Normal.
A-27b.	F.	3 mos.	1.53	2, 4, '07.	L. lobe	0.15	Reddish, transl.	Firm	Reduced
A-123a	M.	52 days.	1.4	7, 5, '08.	L. lobe	0.195	Reddish, transl.	Firm	Normal.
A-123b.	M.	3½ mos.	2.5	1, 6, '08.	One-half of r. lobe	0.100	Reddish, transl.	Firm	Normal.
A-123c.	M.	8⅝ mos.	8.1	7, 12, '08.	All of r. lobe	0.600	Gray, red.	Moderate.	None
A-63a	F.	Middle.	12.7	17, 4, '07.	L. lobe	14.25	Yellowish, transl.	Firm	Normal.
A-63b.	F.	Middle.	12.7	22, 5, '07.	R. lobe	14.00	Yellowish, transl.	Firm	Normal.
A-95a	F.	Middle.	5.9	11, 5, '07.	L. lobe	5.1	Yellowish, transl.	Firm	Normal.
A-95b.	F.	Middle.	5.7	6, 6, '07.	R. lobe	3.4	Yellowish, transl.	Firm	Normal.
A-104a	F.	Middle.	7.71	10, 9, '07.	R. lobe ⅔ l. lobe.	1.7 1.45	Yellowish, transl.	Firm	Normal.
A-104b.	F.	Middle.	7.7	4, 1, '08.	Part of l. lobe.	2.25	Reddish, transl.	Firm	Visible.
A-104c.	F.	Middle.	7.7	7, 1, '08.	Remains of l. lobe.	0.230	Reddish, transl.	Firm	Visible.
A-106a	F.	Middle.	11.8	5, 6, '07.	R. lobe	29.5	Clear, brownish-yellow.	Firm	Normal.
A-106b.	F.	Middle.	9.52	15, 7, '07.	½ l. lobe	15.0	Clear, brownish-yellow.	Firm	Normal.
A-106c.	F.	Middle.	9.50	10, 9, '07.	½ of remaining part of l. lobe.	3.0	Reddish, yellow.	Moderate.	Reduced
A-106d.	F.	Middle.		7, 12, '07.	Remains of l. lobe.	4.5	Reddish, opaque.	Soft	Just visible.
A-122a	F.	2 mos.	1.8	7, 5, '08.	Part of l. lobe.	2.2	Yellow, transl.	Firm	Normal.
A-122b.	F.			21, 5, '08.	Part of l. lobe.	2.5	Yellow transl.	Firm	Normal.
A-122c.	F.		2.3	1, 6, '08.	Part of l. lobe.	1.0	Yellow, transl.	Firm	Normal.
A-122d.	F.			12, 6, '08.	Part of l. lobe.	1.8	Yellow, transl.	Firm	Normal.
A-122e.	F.	3 mos.	2.9	17, 6, '08.	Entire r. lobe.	10.5	Yellow, transl.	Firm	Normal.
A-64a	M.	Pup.	2.9	17, 4, '07.	L. lobe	2.25	Reddish, opaque.	Moderate.	Reduced
A-64b.	M.		4.1	5, 6, '07.	R. lobe	2.3	Reddish, transl.	Firm	Normal.
A-94a	F.	Middle.	2.15	11, 5, '07.	L. lobe	1.5	Reddish, transl.	Firm	Normal.
A-94b.	F.	Middle.	1.95	25, 5, '07.	R. lobe	1.0	Reddish, transl.	Firm	Normal.
A-112a	F.	Young adult.	5.4	15, 1, '08.	L. lobe and ⅔ of r. lobe.	4.15	Reddish, transl.	Moderate.	Reduced
A-112b.	F.	Young adult.	5.4	25, 3, '08.	Part of r. lobe.	?	Reddish. transl.	Firm	Normal.
A-112c	F.	Young adult.	5.9	7, 12, '08.	All of r. lobe	0.250	Reddish. opaque.	Moderate.	Visible.
A-74a	F.	Young.	5.44	25, 4, '07.	L. lobe	3.6	Reddish, opaque.	Moderate.	Reduced
A-74b.	F.	Young.	6.35	1, 6, '07.	R. lobe	2.8	Reddish. opaque.	Moderate.	Reduced
A-126a	M.		?	2, 6, '08.	L. lobe 5.6 r. lobe	13.0 12.8	Reduish, transl.	Moderate.	Visible.
A-126b.	M.	2 years.	?	29, 6, '08.	Remains of r. lobe.	3.3	Reddish brown.	Moderate.	Visible.

IODIN WAS NOT GIVEN.

Histologic Diagnosis.	Iodin per gm., dried.	Iodin per gm., Moist	Complicating Factors in Experiment.	Remarks.
Normal	0.886	0.248	None.	
Early gland. hyperplasia.	1.520	0.253	Pneumonia.	
Normal	6.921	1.384	None.	
Normal	.....	.....	None.	
Marked gland. hyperplasia.	0.115	0.025	None.	
Colloid	1.246	0.298	None	*
Colloid	0.323	0.092	None	Killed 5, 22, '07.
Colloid	1.076	0.251	None.	
Colloid	0.719	0.163	None	Killed with chloroform 6, 6, '07.
Colloid	2.738	0.510	None	Bitch gave birth to 5 pups 5, 17, '07. Impregnated again 9, 7, '07.
Colloid, early gland.				
Colloid, early gland.	.....	.....	Tetany	Died 1, 7, '07 of tetany.
Colloid	0.308	0.033	None.	
Colloid	0.554	0.096	None.	
Colloid, mod. gland. hyperplasia	0.554	0.099	None.	
Colloid, mod. gland. hyperplasia.	0.115	0.022	Probably myxedema.	Bitch died 1, 21, '08—1½ months after last operation. Accessory thyroids present.
Colloid	1.520	0.370	None	On admission neck brown from iodin.
Colloid	1.350	0.384	None.	
Colloid	1.621	0.437	None.	
Colloid	1.262	0.350	None.	
Colloid, gland	1.615	0.361	None	Killed June 17 by another dog; neck terribly torn and r. thyroid lobe hanging from wound.*
Early gland. hyperplasia.	0.300	0.051	None.	
Colloid	2.326	0.451	None	Killed with chloroform 6, 6, '07.
Early gland. hyperplasia.	0.657	0.122	None.	
Early gland. hyperplasia.	1.024	0.215	$HgCl_2$ poisoning	Died May 25 of acute $HgCl_2$ poisoning.
Early mod. gland. hyperplasia.	0.332	0.078	Pregnant.	
Colloid	.....	.....	Pregnant	Gave birth to 2 pups 3, 15, '08. Gave birth to 5 pups 10, 29, '08.
Colloid, mod. marked gland. hyperplasia.	0.128	0.030	None	Tetany developed during second pregnancy; controlled by $CaCl_2$; developed myxedema after last operation
Mod. gland. hyperplasia.	0.521	0.072	None.	
Colloid, early gland. hyperplasia.	1.452	0.275	None	Killed with chloroform 6, 1, '07.
Colloid, mod. gland. hyperplasia.	0.448	0.098	None.	
Colloid, early mod. gland. hyperplasia.	0.560	0.114	Slight wound infection; cleared up quickly.*	Died while taking ether at 2d operation

TABLE 2.—EXPERIMENTS IN WHICH

Case No.	Sex.	Age.	Weight	Day, Month, Year of Operation.	Part Removed.	Weight of Gland Removed.	Color.	Consistency.	Colloid.
A-121a ...	M.	Middle. .	7.3	22, 4, '08..	Part of r. lobe	4.6	Reddish Yellow.	Moderate..	Visible.....
A-121b....	M.	Middle. .	.....	28, 4, '08..	Part of r. lobe.	7.6	Reddish yellow.	Moderate..	Visible.....
A-121c ...	M.	Middle. .	.....	9, 5, '06...	Part of r. lobe.	6.4	Reddish, transl.	Moderate..	Visible.....
A-121d....	M.	Middle. .	.....	21, 5, '08..	Part of l. lobe.	3.6	Reddish, transl.	Moderate..	Normal.....
A-121e ..	M.	Middle. .	8.7	2, 6, '08...	Part of l. lobe.	1.2	Reddish, transl.	Moderate..	Normal.....
A-121f ..	M.	Middle.	.....	12, 6, '08..	Part of l. lobe.	4.85	Reddish, transl.	Moderate..	Normal.....
A-121g	M.	Middle. .	.....	27, 6, '08..	Part of l. lobe.	4.2	Reddish, transl.	Moderate..	Normal.....
A-121h....	M.	Middle. .	.....	10, 7, '08..	Part of l. lobe.	2.0	Reddish, transl.	Moderate..	Normal.....
A-121i . ..	M.	Middle. .	10.9	13, 9, '08..	Part of l. lobe.	0.5	Reddish, transl.	Moderate..	Reduced ..
A-121j . ..	M.	Middle .	12.1	1, 1, '08...	Part of l. lobe.	0.8	Reddish, transl.	Moderate..	Normal.....
A-121k....	M.	Middle .	12.0	22, 12, '08.	Part of l. lobe.	0.855	Gray, red, transl.	Moderate..	Reduced ..

weeks; one was fed pure iodin by mouth, one ferrous iodid by mouth, and the other was kept as a control. We also took three pups raised in the laboratory with histologically normal glands and fed the same amount and kinds of iodin to them. In the goitrous pups the loss of weight was very rapid (one-twelfth of body weight in five days) in those fed iodin, and one-fortieth in the pup used as a control. On the other hand, the normal pups continued to gain in weight, whether fed iodin or not.

This brings up a very important, though well-known, observation, namely, that iodin administered to dogs with hyperplastic thyroids has a physiological action like the desiccated thyroid; i. e., it rapidly reduces the body weight, while iodin administered to normal dogs does not. Without further data than our anatomic observations we advance the following possible explanation for this phenomenon, which has long been known to students of human goiter: In the hyperplastic glands their ability to take up iodin is greatly increased, owing to the greatly increased blood supply and the increased epithelial surfaces of the gland, and the excretory apparatus (whether through the venous or lymph channels) is also greatly increased so that the ability of the gland to give off the iodized protein substance is increased to practically the same extent as is the ability to take iodin from the blood, and until this excretion can be lessened the organism is receiving, in effect, excessive doses of the physiologically active substance. As will be recalled from the anatomic

IODIN WAS NOT GIVEN—Continued.

Histologic Diagnosis.	Iodin per gm., Dried.	Iodin per gm., Moist.	Complicating Factors in Experiment.	Remarks.
Colloid, mod. gland. hyperplasia.	0.269	0.059	None.	
Colloid, mod. gland. hyperplasia.	0.455	0.099	None.	
Colloid, early mod. gland. h'perplasia.	0.692	0.167	None.	
Colloid, early gland. hyperplasia.	1.838	0.520	None.	
Colloid, early gland. hyperplasia.	1.774	0.446	None.	
Colloid, early gland. hyperplasia.	1.427	0.369	None.	
Colloid.....	2.170	0.550	None.	
Colloid, early gland. hyperplasia.	1.091	0.188	None.	
Colloid, early gland. hyperplasia.	1.082	0.196	None.	
Colloid.....	1.925	0.513	None.....	From 10, 3, '00, to 10, 25, '08, dog was given 15 c.c. syr. ferr. iodid by mouth. Histology: Colloid gland.
Colloid, early gland. hyperplasia.	1.540	0.305	None.....	Developed tetany 12, 27, '08; controlled by $CaCl_2$ and, save for tetany, in excellent condition 1, 26, '09.

studies, the body proceeds to accomplish this end by gradually inducing obliterating endarteritis accompanied by a lessening of the size of the veins and lymphatic channels from the gland so that these changes are quite evident when the gland has reached the colloid state. (This process has also been recognized and described by v. Bruns,[3] by Oelsner[4] and De Ligneris.[5]) And, as is well known, the administration of small doses of iodin (not in the form of desiccated thyroid) to normal or colloid glands does not occasion a noteworthy loss of weight. Indeed, clinically, in dogs it induces an increase in weight. Whether these anatomic changes in the vessels accompanying the process of involution (reversion) may be interpreted truthfully as we have here hypothesized is for future experiment and observation to decide. It is, indeed, very suggestive of such a physiologic rôle and may be made use of in clinical experiments with advantage, as we have already done, namely, that of beginning with very small doses of iodin in the hyperplasias and gradually increasing the dosage as the glands approach the quiescent or colloid state. We may add also that in exophthalmic goiter we have used the same method and with it have not seen the well-known untoward effect of

3. Bruns: Beitr. z. klin. Chir., 1896, xvi, 521.

4. Work done under T. Kocher and referred to by him in Arch. f. klin. Chirurg., 1908, lxxxvii, 131.

5. De Ligneris: Dissertation, Berne, 1907.

either desiccated thyroid or of iodin, as these substances usually have been administered in such cases. Thus iodin has a powerful drug action, this action varying with the dosage and with the degree of active hyperplasia of the thyroid and in its administration in all cases of goiter, whether in man or animals, two points should always be borne in the mind, viz.: (1) Small doses of iodin accomplish better thyroid effects than larger doses, whether the gland is normal, colloid or hyperplastic; (2) and, while in normal or colloid glands large doses of iodin (not in the form of desiccated thyroid) usually have no untoward thyroid effects, in the case of actively hyperplastic glands the dose must always be inverse to the degree of thyroid hyperplasia.

To sum up, then, we have observed:

1. The tendency of all active hyperplasias is to revert spontaneously to colloid glands, and this change is hastened or delayed by the presence or absence of iodin. The amount of iodin given is of little consequence in normal and colloid glands, but of the greatest significance in the active hyperplasias.

2. The ability of the glands to take up iodin does not depend so much on the form, mode or amount of its administration as it does on the degree of active thyroid hyperplasia.

3. There is a minimum amount of thyroid tissue below which iodin does not protect against compensatory hyperplasia. This limit is roughly the same whether colloid or normal gland.

It is probable that desiccated thyroid would further inhibit the hyperplasia, though we have no experiments on this point. Such a finding would add to the general belief that there are other activities of the thyroid than that associated with the elaboration of the iodized protein.

EXPERIMENTAL CONGENITAL HYPERPLASIA OF THE THYROID IN DOGS

So far as is known to us, Halsted[6] was the first to produce and to recognize the experimental production of congenital thyroid hyperplasia in dogs. His observations were made in 1888-9 and included three litters of goitrous pups from three different bitches. All these bitches had had part of their thyroids removed (from one to one and a third lobes) prior to impregnation. The thyroids were, in two litters, twenty times and, in the other, about twelve times larger than normal pups' thyroids. These pups' thyroids showed no differentiation into colloid containing alveoli, as is the case in normal glands, but in general the alveoli were small, undistended tubular structures, lined with cubical

6. Johns Hopkins Hosp. Rep., 1896, i, 399.

epithelium. The whole structure much resembled that of the parathyroid gland.

Following this, Edmunds[7] was able to get a similar result in one experiment. Thus far we have seen no records of attempts to produce litters of normal pups from bitches which have previously given birth to goitrous ones, or *vice versa*. It is on this phase of the subject that we wish to record our observations.

Dog A-17.—A female dachshund admitted Jan. 20, 1907, weight 5.4 kg. Excellent condition. Thyroid lobes not palpable.

Jan. 22, 1907: Under ether anesthesia the right lobe was removed, weighing 0.7 gm. Excellent recovery. Gross description of the gland removed: Firm, yellowish translucent, colloid visible. Normal vascularity.

Histologic Diagnosis.—Normal-early glandular hyperplasia. Iodin determination not made. (Specimen lost by accident).

Jan. 26, 1907: Wound healed.

January 26 to February 7 inclusive: 200 mg. of iodin were given in the food.

February 22, five pups were born, one still-born. The subsequent histories of these five pups are tabulated in Table 3.

TABLE 3.—PUPS OF DOG A-17.

No. of Puppy.	Weight. Gm.	Sex.	Age.	Day, Month, Year of Operation.	Portion of Thyroid Removed.	Histologic Diagnosis.	Iodin Content.	Remarks.
A-17α..	212	?	0	.....	.....	Normal fetal thyroid.	?	Still-born.
A-17β..	210	F.	3 days.	25, 2, '07..	Both lobes.	Normal fetal thyroid.	Trace.....	Died 18, 2, '07; unable to nurse.
A-17γ..	290	?	9 days.	3, 3, '07...	Left lobe..	Normal fetal thyroid.	Trace.....	Died 4, 3, '07.
A-17δ..	290	F.	9 days.	3, 3, '07...	Right lobe.	Normal fetal thyroid.	?	Died 9, 3, '07; wound infection.
A-17ε..	?	M.	26 days.	Autopsy.	Both lobes.	Normal.	?	Died 20, 3, '07; kerosene poisoning.

March 15: The mother had scabies; had lost some weight. Dog was chloroformed to death. Weight at death 5 kg. Left lobe of thyroid was removed at autopsy; weight, 0.65 gm.

Gross Description of Left Lobe.—Yellowish, translucent. Abundant colloid. Capsule and vessels normal.

Histologic Diagnosis.—Pure colloid gland (goiter).

Iodin per gm., dry = 4.615 mg. Iodin per gm., fresh = 1.093 mg.

Dog A-104.—Mongrel fox terrier admitted May 16, 1907. Pregnant. Weight, 7.71 kg. Good condition. The thyroid lobes were not palpable.

May 17: Five pups born.

May 21: Four pups alive and in good condition.

August 27: All pups in good condition.

The subsequent histories of these pups are tabulated below.

September 7: Bitch impregnated by non-goiterous fox terrier.

September 10: Under ether anesthesia the entire right lobe, weighing 1.7 gm., and approximately two-thirds of left lobe, weighing 1.45 gm., were removed.

7. Lancet, London, 1901, i, 1451.

Gross Description of Gland Removed.—Yellow, translucent. Consistency firm. Vascularity normal. Capsule thin and delicate. Colloid abundant.

Histologic Diagnosis.—Pure colloid gland (goiter).

Iodin per gm., dry = 2.739 mg. Iodin per gm., fresh = 0.510 mg.

September 16: Dressings removed. Wound healed; had had no evidence of tetany.

October 21: Bitch pregnant.

TABLE 4.—PUPS OF DOG A-104, FIRST LITTER.

No. of Puppy.	Day, Month, Year of Operation.	Age.	Sex.	Weight, Kg.	Portion and Weight of Thyroid Removed.	Histologic Diagnosis.	Remarks.
Pup 1 (T-15)	27, 8, '07	102 days	F.	1.6	Left and ⅓ of right lobe.	Normal	Ether anesthesia.
Pup 1 (T-15)	4, 1, '08	232 days	F.	3.2	Remainder of rt. lobe, 0.150 gm.	Early gland. hyperplasia.	Ether anes.; died 7, 1, '08; tetany.
Pup 2 (T-24)	6, 9, '07	112 days	M.	2.8	Lt. lobe, 0.350 gm. ⅓ rt. lobe, 0.050	Normal	Ether anesthesia.
Pup 2 (T-24)	4, 1, '08	232 days	M.	6.4	Part of rt. lobe, 0.275 gm.	Early gland. hyperplasia.	Ether anesthesia.
Pup 2 (T-24)	20, 12, '08 (Autopsy).	279 days	M.	7.0	Remainder of rt. lobe, 0.150.	Mod. gland. hyperplasia.	Distemper — chloroformed.
Pup 3 (T-25)	6, 9, '07	112 days	F.	1.8	Left lobe, 0.350.	Normal	Ether anesthesia.
Pup 3 (T-25)	30, 10, '07 (Autopsy.)	139 days	F.	2.6	Right lobe, 0.355.	Mod. gland. hyperplasia.	Killed by another dog.
Pup 4 (T-51)	17, 10, '07 (Autopsy.)	153 days	M.	2.3	Left lobe, 0.700.	Normal	Killed by another dog. (Kept as control.)

November 9: Whelped four pups, the subsequent histories of which are tabulated in Table 5.

December 22: Bitch in excellent condition.

January 4, 1908: Under ether anesthesia a part of the remaining portion of the left lobe, weighing 2.25 gm., was removed, leaving a piece of thyroid tissue about the size of a small pea. The parathyroid was not seen.

TABLE 5.—PUPS OF DOG A-104, SECOND LITTER.

No. of Puppy.	Day, Month, Year of Operation.	Age.	Sex.	Weight, Gm.	Portion and Weight of Thyroid Removed.	Histologic Diagnosis.	Remarks.
Pup 1 (T-73)	14, 11, '07 (Autopsy.)	5 days	F.	320.0	Both lobes, 0.105 gm.	Early gland. hyperplasia.	Chloroformed. (Control.)
Pup 2 (T-96)	7, 12, '07 (Autopsy.)	28 days	F.	960.0	Both lobes, 0.400.	Early gland. hyperplasia.	Killed by another dog.
Pup 3 (T-97)	7, 12, '07 (Autopsy.)	28 days	F.	910.0	Both lobes, 0.305.	Early gland. hyperplasia.	Killed by another dog.
Pup 4 (T-2)	24, 12, '07 (Autopsy.)	45 days	F.	1.110	Both lobes, 0.450.	Mod. gland. hyperplasia.	Killed by another dog.

Gross Description of Gland Removed.—Quite firm and vascular and showed considerable regeneration of the thyroid beyond the old suture line. Color red-translucent. Colloid visible.

Histologic Diagnosis.—Colloid-early glandular hyperplasia. No iodin determination.

Jan. 7, 1908: Dog died during the night of tetany. Autopsy showed evidence of salivation. Gastric dilatation. Other tissues normal. Remaining piece of thyroid weighed 0.230 gm. and on histologic examination the ligature was found to have included and caused necrosis of what was probably the only remaining parathyroid.

Dog A-112.—Female mongrel, admitted Jan. 11, 1908. Weight, 5.3 kg. Nutrition good. Thyroid lobes not enlarged.

January 12: Impregnated by a healthy fox terrier.

January 15: Under ether anesthesia the whole left and approximately two-thirds of the right lobe were removed. The total gland removed weighed 4.15 gms. Good recovery.

Gross Description of Gland Removed.—Dark red in color. Moderate consistency. Colloid barely visible. Lobes appear somewhat enlarged. Moderately vascular.

Histologic Diagnosis.—Moderate glandular hyperplasia.

Iodin per gm., dried = 0.332. Iodin per gm., fresh = 0.078.

January 18: Jaws slightly swollen; otherwise condition good.

January 20: Swelling of jaws had disappeared. Appetite good.

January 22: Bandage and stitches removed. Wound healed. The dog received no iodin except what might have been obtained from the food.

March 15: Two pups were born, one still-born; mother in good condition. The histories of these pups are tabulated in Table 6.

TABLE 6.—PUPS OF DOG A-112, FIRST LITTER.

No. of Puppy.	Day, Month, Year of Operation.	Age.	Sex.	Weight, Gm.	Portion and Weight of Thyroid Removed.	Histologic Diagnosis.	Remarks.
Pup 1.....	15, 3, '08. (Autopsy.)	0	?	280.0	.....	Fetal type of hyperplasia.	Still-born.
Pup 2.....	7, 5, '08.....	52 days..	M.	1.35	Left lobe, 0.195.	Colloid.....	Fed iodin; ether anesthesia.
Pup 2.....	1, 6, '08.	77 days..	M.	?	½ of right lobe, 0.100.	Colloid.....	Fed iodin; ether anesthesia.
Pup 2.....	7, 12, '08	267 days.	M.	8.1	Remainder of rt. lobe, 0.600.	Colloid—marked gland. hyperplasia.	11, 3, '09, no tetany, no myxedema, normal.

March 25: Under ether anesthesia approximately one-half of the remaining portion of the right lobe was removed. Recovery from operation good. Piece removed had a normal gross appearance.

Histologic Diagnosis.—Pure colloid gland (goiter). No iodin determination.

March 26, 9 a. m.: Dog in violent tetany. Respiration 180-200 per minute. Mouth gaping. Pulse could not be counted. Tongue protruding and of a very bright red color. Profuse salivation. Dog lay on its side. All muscles tense with intermittent general tetanic seizures. Was given 5 c.c. of a 5 per cent. calcium chlorid solution in one-half pint of milk by a stomach-tube. At 4 p. m. dog was able to walk, though very weak.

March 27: Repeated the dose of calcium chlorid with milk. Dog still had slight muscular twitchings. Respiration 32. Pulse 130.

April 1: Calcium chlorid stopped. Apparent recovery from tetany. Bandage removed, together with stitches. Wound healed.

April 6: No evidence of tetany, though five days have elapsed since calcium chlorid was stopped.

July 3: Dog and pup in good condition. No evidence of scabies, but a prophylactic application of sulphur ointment was given.

September 1: Dog in excellent condition.

October 1: Sulphur ointment again applied.

October 15: Dog pregnant.

October 29: Gave birth to five pups.

October 30: One pup, weight 115 gm., chloroformed to death. Thyroid lobes histologically normal.

November 2: One pup, weight 260 gm., chloroformed to death. Thyroid lobes histologically normal.

November 3: Mother in violent tetany, given 50 c.c. of a 5 per cent. solution of calcium chlorid with relief in two hours.

November 19: No tetanic symptoms since November 3. 5 c.c. of calcium chlorid solution had been given daily.

December 3: Mother and three pups normal. Had weaned the pups.

Summarizing these cases, we find that A-17 gave birth to normal pups after one lobe had been removed and iodin administered. The remaining lobe returned to the colloid state, while the first lobe removed was histologically a *normal-early* glandular hyperplasia.

In A-104 a litter of normal pups was born shortly after admission; then after nearly four months the dog was again impregnated and one and two-thirds thyroid lobes removed, which histologically were pure colloid glands. In the second litter, the pups' thyroids were slightly enlarged and histologically were in a state of early glandular hyperplasia. The remaining portion of the mother's thyroid had also undergone hyperplasia.

In A-112, immediately after impregnation, one and two-thirds lobes were removed, which histologically were in the state of moderate glandular hyperplasia. Of the two pups born, one died at birth and its thyroid was slightly enlarged and histologically showed only cylinders of columnar cells, with no evidence of colloid (fetal type of hyperplasia likened by Halsted to parathyroid tissue). The mother and pup were given iodin. The pup was reared. The second litter of pups from this bitch (A-112) was normal.

These cases, in so far as they show a repetition of Halsted's results, are positive, but they are only suggestive of the inhibiting effect of iodin. They do not eliminate the possibility and, indeed, the probability of other factors than iodin as determining the fetal thyroid reaction. We believe that iodin is the greatest single factor, but that the general food and the general hygienic surroundings are also of great importance, since all the cases of congenital goiter examined show general nutritional disturbances, as anemia, bone changes, etc. Such cases in human pathology have usually been included under "fetal rickets." This fetal thyroid hyperplasia, so far as our observations have extended, seems to

be identical in its anatomic and physiologic characteristics with compensatory hyperplasia following partial removal, and it is likewise identical histologically with the naturally occurring hyperplasias, whether of prenatal or postnatal origin. Iodin has similar inhibiting and involuting (reverting) effects in all these forms of hyperplasia.

Finally, it seems advisable to add some account of the clinical phenomena accompanying these various anatomic conditions of the thyroid, in order that the rather disconnected anatomic, chemical and general biologic data discussed on the preceding pages may be utilized for clinical inference. Again the anatomic grouping must be followed.

1. *Normal Glands.*—Animals with normal thyroids obviously do not concern us.

2. *Colloid Glands.*—Animals with colloid glands are, as a rule, adults (unless treated) and present no symptoms referable to the thyroid, save that the glands are usually enlarged, and, for this reason, one may observe mechanical (pressure) effects, although in quadrupeds this is extremely rare. All animals (sheep and dogs) whose glands were pure colloid were clinically in excellent health. This applies to the colloid glands experimentally produced (by the direct administration of iodin, by food or otherwise), as well as the natural occurring ones.

3. *Hyperplasias.*—The great majority of all animals (sheep, dogs, cats, horses, hogs and cattle) whose glands were histologically in the state of active hyperplasia showed no symptoms which would distinguish them from normal animals by the ordinary methods of examination. This statement is of importance when one recalls that 90 per cent. of the dogs and 50 per cent. of the sheep and cattle of this locality show hyperplastic changes of a greater or lesser degree. On the other hand, there is a degree of hyperplasia which, when present, is always accompanied by clinical manifestations. These clinical manifestations are of different degrees, reaching their highest in the true cretins which die shortly after birth, thence shading off gradually to the limit of detectability. We have used the term "cretinoid" in order to include the several degrees of severity of the symptoms.

All these animals are young (calves, lambs or puppies). In the worst forms the animals die immediately after birth. Such subjects show poorly developed, hairy coats (thin, coarse), a high degree of anemia and deficient calcification of the bones, but with no reduction in the subcutaneous fatty tissue. These animals, as a rule, have much-enlarged thyroids of the glandular-vascular type with promient lymph glands, thymus and spleen. In dogs, the most common types at the laboratory have been the less severely affected subjects—those which

would eventually recover spontaneously. Farmers in Michigan have told us that lambs usually recover if able to suckle. We have found the same to be true of dogs. In these milder cases one notes the following characteristics: The hair is dry, coarse and partially furred. The palpebral fissure is narrow. The eyes are weeping and dull. The heart is hypertrophied. The rate is rapid and the beat forcible. On slight exertion, back pulsation in the neck veins occurs and the thyroid lobes become acutely swollen with blood. This may produce syncopal attacks in which the animal may die. The epiphyses of the bones are enlarged. The mucous membranes are very pale, almost blanched. So far as we have observed, the appetite is good and the general body bulk is quite or above the average weight. The gait is slow, unsteady, awkward, and mentally they are extremely dull. We have never observed true exophthalmos, although we have imagined in some cases that the eyes were slightly more prominent than in normal pups. These two types illustrate the severest and the moderate degrees. The milder forms down to clinically normal dogs show the same kind of manifestations, the difference being of degree. Excellent and much fuller descriptions of the phenomena in lambs and calves may be obtained from reports by Davis,[8] Seligmann[9] and Campbell.[10]

8. Davis: Vet. Jour. and Ann. Comp. Path., 1898, xlvii, 25.
9. Seligmann: Tr. Path. Soc. Lond., 1903-4, lv, 1.
10. Campbell: Tr. Med. and Phys. Soc., Calcutta, 1833-4, vii, 1.

OBSERVATIONS ON A CHILD WITH A GASTRIC FISTULA IN RELATION TO RECENT ADVANCES IN THE PHYSIOLOGY OF GASTRIC DIGESTION

R. S. LAVENSON, M.D.
PHILADELPHIA

There is no field of medicine in which more activity has been displayed in recent years than in the physiology of digestion. Processes that had previously been considered of the utmost simplicity have been shown to be complex and intricate. Both secretory and motor functions of the digestive organs have been demonstrated to be remarkably selective and purposive and to be subject to interrelations well beyond our previous conceptions. Many of the newer discoveries have been the result of the activity of Pawlow and his followers, and of the methods devised by them, which permit a much more accurate determination of the functions of the digestive organs than had previously been possible. Most of the facts that have been determined have been the result of animal experimentation; though some observations have been made on suitable human subjects, they have not as yet been so numerous as to make further contributions to the subject undesirable. With this in mind, I made search for an appropriate subject on whom to conduct observations.

As the majority of patients on whom gastrostomy is performed suffer from malignant growths, which would be likely, through either their local or their constitutional effects, to cause gross abnormalities of the gastric functions, such patients would obviously be unsuitable for the observations that I desired to conduct. I succeeded in finding a suitable subject in the person of a girl, 14 years of age, on whom a gastrostomy had been performed for a complete benign cicatricial stenosis of the esophagus. This procedure was carried out eleven years ago by Dr. John H. Jopson, to whom I wish to express my obligation for bringing the patient to my notice. The esophageal obstruction, which resulted from the drinking of lye, is situated at about the level of the bifurcation of the trachea. The patient, living in one of the rural districts of Pennsylvania, has grown into vigorous adolescence, feeding herself by means of a small stomach-tube, one end of which is inserted into the gastric fistula. The other end is tied with a string about the neck, so that no portion of the tube is seen except when the patient eats. During meals she partakes only of liquid and semisolid foods, masticating and swallowing in

the usual way until about three ounces have been taken. She then places the upper end of the tube in her mouth and, with a slight voluntary effort at regurgitation, forces the food from the pharynx and esophagus into the mouth and down through the tube into the stomach. This process is repeated until the meal is completed. The patient apparently enjoys her meals, and possesses the usual childish fondness for sweets and other dainties. At my request, she was brought to the University Hospital, where I conducted the observations to be subsequently described.

As is almost too well known to warrant repetition, it was the remarkable work of Pawlow[1] that has established, in great part, our present conceptions of the physiology of digestion. For the proper comprehension of certain terms and references to be used in this paper it will be well to describe briefly two of the procedures instituted by Pawlow. One of these consisted in performing a gastrostomy on a dog and subsequently sectioning the esophagus in the neck; the gastrostomy wound was so treated as to form a permanent fistula; the lower end of the sectioned esophagus was closed and tucked in the wound, while the edges of the upper end, that communicating with the pharynx, were stitched to the skin so as to form a permanent esophageal fistula. By means of this combination of operations, communication between the mouth and stomach is completely destroyed. Though the dog can chew and swallow food, it passes out of the esophageal fistula instead of into the stomach. At the same time any juice secreted in the stomach can be collected, uncontaminated by food or saliva. Feeding dogs previously operated on in this way constitutes a "Scheinfütterung" or "false feeding." A second important operation devised by Pawlow consists in establishing practically two gastric cavities. The smaller of these, which communicates with the external surface of the body, is so separated from the larger cavity that no substances can pass from the one to the other. Its nerve and blood supply are, however, retained so that any influence acting on the main stomach calls forth the same response in the smaller one. As the latter communicates with the abdominal surface its secretion can be easily collected. It was by means of this procedure that Pawlow investigated the character, rate and amount of the gastric secretion induced by various foods.

Probably the most important fact established by Pawlow was that there are two distinct classes of excitants to the flow of gastric juice. The first and most important of these consists of the psychic excitants, those which by appealing to one of the senses or higher mental faculties

1. Die Arbeit der Verdauungsdrüsen, Wiesbaden, 1898.

induce appetite and cause the flow of gastric juice. A stimulus that appeals to the psychical processes by means of the senses of taste or smell might be called a psychic stimulus; one inducing appetite by a more indirect route, by appealing to the mental processes by means of the senses of sight, hearing or touch, might be called an indirect, or associated, psychic stimulus. In man, even the higher mental processes, memory and imagination, come well within the group of psychic stimuli. The second group of excitants of gastric juice consists of the chemical stimuli—those that act only by direct contact with the gastric mucosa. Incidentally, Pawlow showed that mechanical stimuli, previously thought to be of profound influence, are totally incapable of inducing gastric secretion.

I had hoped to be able to demonstrate on my patient the efficiency of psychic stimuli in inducing gastric secretion, by appealing to the various senses with food and collecting the gastric secretion by means of a catheter introduced into the stomach through the fistula. I soon found, however, that this was impossible. Although the patient desired to lend herself completely to the experiment, she could not overcome the fact that it was an experiment and distasteful to her. This mental attitude was apparently sufficient to inhibit entirely the natural effect of these psychic stimuli. The very fact that the stimuli are psychic makes them subject to untold variations; and any other psychic process working at cross-purposes to them is apparently able to nullify them completely.

Pawlow encountered numerous instances of this nature in his work on dogs. Many of the animals, by reason of their not taking kindly to the experiments, had to be discarded as totally unfit for the proposed observations. Others that ordinarily manifested a vigorous flow of gastric juice, when irritated or angered or otherwise disturbed, failed entirely to manifest the usual secretion.

The influence of the emotions on gastric secretion was strikingly seen in some observations of Bickel and Sasaki.[2] They had in their laboratory a dog with an esophageal and a gastric fistula, on which they had been making false-feeding observations. The animal, which was not of an especially friendly temperament, was found to work himself into a violent frenzy at the sight of a cat that happened to be brought into the laboratory. Bickel and Sasaki used this phenomenon to demonstrate the influence of emotional excitement on gastric secretion. In a control false-feeding experiment as ordinarily conducted, 66.7 c.c. of gastric juice were collected in the first twenty minutes after the feeding. On a subse-

2. Bickel and Sasaki: Deutsch. med. Wchnschr., 1905, xxx, 1829.

quent day the dog was allowed to excite himself by watching the cat for a period of five minutes. After he had become somewhat calmer, a false feeding was administered under the same conditions as in the control experiment; and in the same period of time but 9 c.c. of gastric juice were secreted.

Quite as profound was the effect of excitement in inhibiting a secretion already instituted. The dog was given a false feeding; and in the first five minutes after it 28.5 c.c. of gastric juice were secreted. The cat was then shown to the dog again for five minutes; and the secretion in the subsequent five minutes fell to 3 c.c.

Bogen,[3] in a series of observations to be subsequently described, on a child 3½ years old, found the same inhibitory effect to result from teasing the child or from inducing pain by means of an electric current.

It will serve as of historical interest, as well as a mark of recognition of the powers of observation of a remarkable student of physiology, to state that in 1833 Beaumont[4] observed the same influence in his studies on Alexis St. Martin, as shown by the statement, in speaking of the gastric juice: "Fear and anger check its secretion."

The importance in clinical medicine of these "negative" psychic processes or emotions, which may work at cross-purposes to the "positive" psychic stimuli to gastric juice, can not be overestimated. When we realize their significance, the bearing that worry, anger, grief or excitement may have on the digestive processes becomes at once apparent.

Literature is not wanting in instances among human subjects of the effects of psychic stimuli in inducing gastric secretion. Even long before the days of Pawlow and his experiments, this influence was observed by Richet[5] in a patient with a gastric fistula, and probably even by Beaumont. It is especially as the result of the stimulus given to physiologic research by Pawlow, however, that observations on man have been conducted.

Cade and Latarjet[6] had under observation a patient peculiarly adapted to physiologic observations on gastric secretion. She was a woman, 20 years of age, who, during childhood, had suffered an accident resulting in a hernia of a small portion of the stomach. This hernial sac ruptured spontaneously on the abdominal surface, 2 cm. above the umbilicus. Later, by the growth of inflammatory tissue, the mucous membrane of the smaller portion became totally separated from the mucous membrane

3. Bogen: Arch. f. d. ges. Physiol. (Pflüger's), 1907, cxvii, 150.
4. Beaumont: Physiology and Experiments, Edition 2. Burlington, 1847, p. 81
5. Richet: Jour. de l'anat. et de physiol., 1878, p. 326.
6. Cade and Latarjet: Jour. de physiol et de path. gén., 1905, vii, 221.

of the larger portion of the stomach. As its blood supply and nerve supply were apparently preserved, the condition practically resulted in a human, perfectly functionating Pawlow stomach. Aside from some limited observations on the character of the juice secreted in response to various foodstuffs, Cade and Latarjet were able to demonstrate the effect of psychic stimuli by collecting from the small stomach, during a conversation regarding the patient's favorite foods, more than twice the amount of gastric juice secreted during a similar period while the patient was at mental rest. It is to be regretted that Cade and Latarjet did not make more exhaustive observations, having such an exceptional opportunity as they did.

Bogen conducted observations on a child 3½ years old with a gastric fistula and complete esophageal stenosis. He found, first, that the mastication of meat coming in no wise in contact with the gastric mucosa regularly produced a secretion of gastric juice after a latent period of four to five minutes. The particular object of Bogen's investigations was to determine the efficiency of associated psychic stimuli in producing a gastric secretion. With this end in view, the child was fed with meat at a definite hour each day, and always under the same conditions. Coincidently with the feeding, several blasts, always of the same tone, were blown on a small trumpet. Finally, after this procedure had been repeated something more than forty times in all, the same blast was blown on the trumpet and no meat was fed. Of the ten times that the effect of this associated stimulus was tried, a gastric secretion similar to that obtained when the meat was fed was obtained seven times; in the remaining three times no juice was secreted.

Quite as interesting an instance of an accidentally associated psychic stimulus was observed by Bogen on his patient. He found that after the feeding of meat had been repeated a number of times, occasionally a sudden vigorous flow of gastric juice presented itself some minutes before the meat was given. Watching carefully for the cause of this, Bogen soon found that the stimulus to the flow of juice was the sight of the nurse who brought the child its food conferring with the experimenter preparatory to the expected meal.

A much more complete repetition of the Pawlow experiments on an adult was made by Kaznelson[7] on an individual exceptionally adapted to such observations. The patient had had a gastrostomy performed when she was 15 years old, on account of a complete benign stenosis of the esophagus resulting from the drinking of lye. When she was 23 years

7. Kaznelson: Arch. f. d. ges. Physiol. (Pflüger's), 1907, cxviii, 327.

old, an esophagostomy was performed, resulting in a fistula of the upper patulous portion of the esophagus. Subsequently a long rubber tube with an upper funnel-shaped end was passed down through the pharynx and upper portion of the esophagus and brought out of the esophageal fistula. The lower end of this tube was connected with a tube entering the gastric fistula, so that the patient was able to eat as a normal individual would; the food, after mastication, passing through the tube worn underneath the clothing, instead of through the esophagus. The patient thus presented the same conditions as were instituted by Pawlow on animals for false-feeding experiments, and served very well for observations of this nature.

In these experiments, the lower end of the tube was withdrawn from the stomach; so that the food, after being masticated and swallowed, passed into a receptacle, instead of into the stomach. Kaznelson was able to substantiate on her patient practically all the observations of Pawlow concerning false feeding. The mastication of foodstuffs pleasing to the patient consistently produced an abundant flow of gastric juice. The latent period was approximately five minutes. The simple act of chewing did not call forth gastric juice. Kaznelson found, in addition, as did Pawlow on animals, that in man the acidity of the gastric juice is approximately constant, but that the amount of secretion is subject to great variations.

Umber[8] had similar positive results in a limited number of observations on false-feeding in his patient with a gastric fistula and malignant stenosis of the esophagus. He also had an opportunity of observing the action of an associated psychic stimulus, when his patient suddenly presented a vigorous flow of gastric juice on seeing several pieces of bread and butter unintentionally placed near his bed. In his patient, Umber found the latent period to be but three minutes.

Hornborg[9] had under observation a 4-year-old boy with a gastric fistula and almost complete occlusion of the esophagus, on whom he conducted experiments similar to those already described. He was unable to demonstrate the efficiency of visual stimuli in producing a gastric secretion. This circumstance he attributed to negative psychic stimuli, such as I have described; for when the child was shown food, but was not permitted to eat it, he at once became angry and began to cry. There was, however, always a vigorous flow when the child was permitted to chew food that he liked; although none of it came into contact with the stomach.

8. Umber: Berl. klin. Wchnschr., 1905, xlii, 56.
9. Hornborg: Skand. Arch. f. Physiol., 1903, xv, 209.

Bulawinzew[10] conducted a series of observations on hospital attendants with apparently normal digestions. Test meals of uniform composition were given them, and the acidity and digestive power of the juice removed by means of a stomach-tube were determined. Subsequently the subjects' appetites were excited by appealing to them with stimuli acting on the senses of taste, sight and hearing; after which another meal of the same composition was given, and the acidity and digestive power of the resulting gastric juice again determined. Bulawinzew came to the conclusion that psychic stimuli play an important rôle in the production of gastric juice.

The observations of Pawlow that have apparently found least substantiation in the experiments on human beings are those concerning the effect that mastication has on gastric secretion. Pawlow concluded from his experiments that mastication was powerless to provoke a gastric secretion. His experiments consisted in feeding stones to dogs possessing both esophageal and gastric fistulæ. The observations on man have been conducted almost exclusively by means of the stomach-tube. The investigators who defend the stimulating action of mastication differ as to the particular feature of mastication that exerts the stimulating effect on the gastric secretion. Sticker,[11] as the result of his observations on normal subjects and those with digestive disturbances, concludes that the saliva induced by mastication is the potent factor. Biernacki[12] attributes to the saliva a subordinate rôle, and looks on other undetermined factors associated with mastication as the important ones in inducing the flow of gastric juice; whereas Riegel,[14] Schüle,[14] Riegel and Schreuer,[15] and Troller[16] look on the act of mastication itself as the potent factor in inducing the gastric secretion. Troller, in his remarkable series of investigations conducted on himself, his associates and his patients, showed conclusively that saliva is not a factor in inducing gastric secretion. This he did by permitting patients to chew and insalivate a meal of definite composition. This was not swallowed, but spat out into a receptacle. Later it was introduced, by means of a stomach-tube, directly into the stomach. When subsequently withdrawn, it was found to have produced less secretion than when the same meal was chewed and immediately swallowed.

10. Bulawinzew: Russk. Vrach, 1903, No. 17; Ref. Biochem. Centralbl., 1903, xv, 593.
11. Sticker: Samml. klin. Vortr. (Volkmann's), 1887, No. 297.
12. Biernacki: Ztschr. f. klin. Med., 1892, xxi, 97.
13. Riegel: München. med. Wchnschr., 1899, p. 1489.
14. Schüle: Deutsch. Arch. f. klin. Med., 1901, lxxvii, 111.
15. Riegel and Schreuer: Ztschn. f. diätet. u. physik. Therap., 1900, iv, 462.
16. Troller: Ztschr. f. klin. Med., 1899, xxxviii, 183.

From the results of the investigations mentioned, there is no doubt that the mastication of food produces a more vigorous secretion than would result from the introduction of the same food without the intervention of the act of chewing. I believe, however, that the observers have somewhat misinterpreted their findings. It was found, especially by Troller and by Hornborg, in his observations on his little patient with the gastric fistula, that the chewing of substances of which the patient was fond always produced a greater secretion than did the chewing of an indifferent or a tasteless substance, such as rubber or lemon peel. This is a very definite indication that there was something else than the mere chewing that in part, at least, induced the gastric secretion. This something was undoubtedly the agreeable taste of the substances, which produced a desire on the part of the patient to complete the act of eating them. This desire is nothing more than appetite. In other words, it is the psychic stimulus inaugurated through the sense of taste which induces the flow of gastric juice. In regard to the flow induced by the chewing of tasteless substances, it is not improbable that in this case the more or less conscious association of the act of chewing with the process of which it is commonly a part, eating, results in a psychic stimulus to gastric juice. This association may be thought improbable by reason of an observation of Cohnheim and Soetbeer,[17] who found that the act of sucking in new-born pups induced a flow of gastric juice. However, the pups on which these observations had been made were born at night; and, as they were not taken from their mother until the morning, it is probable that, the pups having obtained nourishment by sucking during the night, the act of sucking became associated with nourishment and thus resulted in a psychic stimulus. Again, it is not improbable that, just as sucking is an instinct, so is the association of sucking and nourishment inherited.

Having encountered the obstacle that I have described in making observations on psychic stimuli with my patient I turned to observations on the chemical stimuli. In order to obtain an insight into the functional activity of the stomach as ordinarily computed, an Ewald test-breakfast was administered, the resulting gastric juice showing a total acidity of 62; free hydrochloric acid, 36. The experiments, lasting in all fourteen days, were conducted in the latter part of the afternoons, about five hours after the patient had eaten. The stomach was first well washed out with water by means of a small stomach-tube with numerous perforations. The stomach was then allowed to become per-

17. Cohnheim and Soetbeer: Ztschr. f. physiol. Chem., 1903, xxxvii, 467.

fectly quiescent before any substances were introduced. The first observation was on the effect of plain, moderately cool, distilled water. One hundred c.c. were introduced through a tube in the fistula; and at the end of ten minutes 40 c.c. were recovered, possessing a total acidity of 9; free hydrochloric acid, 8. This experiment was repeated several times, as were almost all the others, with practically the same results in each case, except for slight variations in the amount of fluid recovered. From this it is seen that water is a definite chemical stimulus to gastric juice in man; this substantiates one of the facts determined by Pawlow in his work on dogs. This effect of water must be kept forcibly in mind in considering the results of the remaining observations; for, as all the substances administered were dissolved in water, the secretion called forth by them must be compared with that induced by a similar quantity of pure water. The low degree of acidity obtained in this, as in the remaining observations, is, in all probability, the result of the short time that the fluids were left in the stomach.

In order to determine the influence of the administration of hydrochloric acid on the gastric secretion, ten drops of dilute hydrochloric acid dissolved in 100 c.c. of water were introduced. Ten minutes later 66 c.c. of fluid were recovered, possessing a total acidity of 19; free hydrochloric acid, 17. As the acidity of the solution of ten drops of dilute hydrochloric acid in 100 c.c. of water is equivalent to 9, it is seen that the acidity of the fluid recovered from the stomach was practically that induced by 100 c.c. of water plus that of the acid introduced. Having repeated this experiment several times with approximately the same result, I believe we are justified in concluding that hydrochloric acid itself, introduced into the stomach, does not induce a secretion of gastric juice.

The influence of native albumin was determined by introducing 4 grams of egg-albumin dissolved in 100 c.c. of water. At the end of ten minutes 34 c.c. were recovered, possessing a total acidity of 10; free hydrochloric acid, 7. It is thus observed that the influence of a solution of egg-albumin is practically only that of an equivalent amount of water.

Quite a different result attended the introduction of a solution of beef-extract. Four grams of one of the commercial beef-juices neutralized and dissolved in 100 c.c. of water were introduced, and at the end of ten minutes 70 c.c. were recovered, possessing a total acidity of 34; free hydrochloric acid, 22. When compared with the acidity of the gastric juice induced by an equal quantity of water it is readily appreciated how powerful a chemical stimulus of gastric juice beef-extracts are. Just what the nature of these substances is has not been deter-

mined. These observations are all in harmony with the results of Pawlow's experiments on the chemical stimulants of gastric secretion in dogs.

The observations on the effect of the bitter stomachics (tincture of nux vomica, tincture of gentian comp.) were exceptionally interesting. Introduced directly into the stomach, they induced no more acid juice than would the same amount of water as that which was introduced with them. When, however, they were given five to ten minutes before a chemical stimulus (solution of beef-extract), they regularly caused a greater secretion than when the latter was given unpreceded by the bitter. Furthermore, a bitter stomachic taken into the mouth caused a greater secretion than if it were introduced directly into the stomach. The most vigorous response I obtained was in a series of observations in which the acidity resulting from a solution of neutralized beef-extract was: Total, 33; free hydrochloric acid, 23. When preceded by 4 grams of tincture of gentian comp., introduced directly into the stomach ten minutes before, the secretion rose to, total acidity, 38; free hydrochloric acid, 26. When the same quantity of gentian was taken into the mouth and kept in the pharynx and upper pouch-like portion of the esophagus for ten minutes preceding the introduction of the beef-extract, the acidity rose to, total, 53; free hydrochloric acid, 40. I subsequently attempted to have the patient take the bitter into the mouth and then introduce it into the stomach to determine whether the combined action was more powerful than either one individually; but the bitter taste was so objectionable that I could not persuade her to do so. From these observations, though not carried to the conclusion that I would desire, it seems evident that bitter stomachics, principally by reason of their action displayed in the mouth and pharynx, have a stimulating effect on the secretion of gastric juice. Their action locally in the stomach, though not so profound as the former, is, nevertheless, definite.

Several observers have come to the same conclusion in regard to the stimulating effect of bitter stomachics. Borrisow[18] found that when he preceded a false feeding in dogs by the application of a bitter stomachic to the mouth and pharynx, over a period of a few minutes, the resulting gastric secretion was more than 30 per cent. greater than occurred when the false feeding was not preceded by the application of the bitter. Hoppe,[19] and also Straschesko,[20] found that a bitter tonic, of itself, induced no secretion; but that when it preceded a false feeding it always

18. Borrisow: Arch. f. exper. Path. u. Pharmakol., 1904, li, 363.
19. Hoppe: Berl. klin. Wchnschr., 1905, xxxiii, 1038.
20. Straschesko: Russk. Vrach, 1905; quoted by Hoppe, Berl. klin. Wchnschr., 1905, xxxiii, 1038.

resulted in an increased secretion of gastric juice. Kaznelson, in her observations on a human subject, came to the same conclusion.

Pawlow, and subsequently several other observers, found that alkalies inhibited gastric secretion. It was impossible, in my patient, to make any reliable observations of the effect of alkalies on secretion. It was of interest, however, to determine their action in regard to gastric motility. A solution of 2 grams of sodium bicarbonate in 100 c.c. of water was introduced, and at the end of ten minutes 9 c.c. of a solution possessing neither free nor total acid was recovered. The bearing that this observation has on gastric motility will be discussed later.

Several other observations, though not of so much significance as those already mentioned, are clinically or physiologically of some interest. Tea, generally employed as an element of the test breakfast, was found to have the same effect in inducing secretion as a similar quantity of water. Various commercial preparations of pepsin were introduced, but were found to have no more effect than that of the amount of water introduced with them. Finally, a nutrient enema was administered while the stomach was empty, and within the first fifteen minutes after its administration 12 c. c. of rather viscid gastric secretion was obtained, possessing a total acidity of 15 and free hydrochloric acid of 11. A similar result was obtained by Umber with his patient.

In addition to the bearing that the foregoing observations have on gastric secretion, several of them permit of interesting deductions on some of the phases of gastric motility. We are indebted, to a great extent, to Cannon[2] for our present conception of the action of the pyloric sphincter and the control that it has on the emptying of the stomach. Cannon's experiments have shown that when food is introduced into the stomach the pylorus closes and remains closed until the necessary conditions are instituted for its periodic opening. These conditions are established by the reaction of the contents on the gastric and duodenal sides of the pylorus. An acid reaction on the gastric side and an alkaline reaction on the duodenal side tend to open the pylorus; whereas an acid reaction on the duodenal side and an alkaline reaction on the gastric side tend to keep the pylorus closed. It is readily appreciated how nicely this mechanism harmonizes with the secretory functions of the stomach and duodenum. When food is taken into the stomach it is retained there until a portion is sufficiently acidified and, we can assume, also peptonized, to be ready for intestinal digestion, when the pylorus opens and lets this portion through into the duodenum. Here, by reason of its acid reaction, this acidified portion tends to the closure of the

21. Cannon: Am. Jour. Physiol., 1907, xx, 283.

pylorus until the alkaline pancreatic juice and bile sufficiently change its reaction to induce the pylorus to open again. By means of this mechanism the food is held in the stomach until gastric digestion is sufficiently advanced; and the duodenum is protected from the danger of having an overwhelming amount of acid chyme poured into it at one time. This mechanism apparently sufficiently explains the operations of the pyloric sphincter under normal conditions, and when the reactions on the two sides of the pylorus are different; that is, either acid on the duodenal side and alkaline on the gastric side, or alkaline on the duodenal side and acid on the gastric side.

It does not, however, give an insight into the relations that are maintained in those conditions in which the same reaction, either acid or alkaline, is present on both sides of the pylorus. Under these circumstances the behavior of the pylorus must depend upon whether the predominating influence rests in the stomach or in the duodenum. It is on this phase of the subject that the observations described above throw some light.

It will be noted, on comparing the secretion resulting from the introduction of the acid solutions and of the alkaline solutions that much larger amounts were returned from the acid than from the alkaline solutions. After a period of ten minutes but 9 c.c. were recovered from the stomach after the introduction of an alkaline solution; whereas, 66 c.c. were recovered after the introduction of an equal amount of an acid solution. These observations were repeated a number of times, with variations of but a few cubic centimeters from the figures given. If the reaction on the gastric side of the pylorus exerted the predominating influence, it would be expected that the acid solution would tend to more frequent or more prolonged opening of the pylorus and, consequently, to the passage of a proportionately greater amount of fluid into the duodenum than occurs after the introduction of the alkaline solution, which would, according to the same hypothesis, tend to keep the pylorus closed. I believe the phenomena that I have observed to be best explained on the following hypothesis:

When an acid solution is in the stomach the phenomena of pyloric discharge observe the mechanism described by Cannon. By reason of the acidity on the gastric side the pylorus opens and a portion of the acid contents is shot into the duodenum. Here, by reason of the same reaction, it closes the pylorus; though acid may still be present on the gastric side. This, then, is an indication of the greater influence of the reaction on the duodenal side, when the reaction on both sides of the pylorus is acid, and the relatively slow discharge of the stomach contents is due

to the time consumed in neutralizing the acidity in the duodenum. When, however, the reaction on the gastric side of the pylorus is alkaline, as in the introduction of a solution of sodium bicarbonate, the original opening of the pylorus can, obviously, not depend on acidity in the pyloric antrum. A portion of the gastric contents must be discharged into the pylorus, in spite of the alkaline reaction on the gastric side. As soon as it arrives in the duodenum its already alkaline reaction combines with the alkaline reaction of the duodenal secretion and tends to either the frequent or the prolonged opening of the pylorus; and, as a result, a much larger amount of fluid passes into the duodenum in a given period of time than when a more acid solution is present in the stomach. From this we draw the conclusion that if the reaction on both sides of the pylorus is alkaline the reaction on the duodenal side is again the predominating one.

If our reasoning thus far is correct (and I believe that it must be to explain the phenomena observed) we may go even farther: If the reaction in the duodenum is the predominating one when the same chemical reaction is present on both sides of the pylorus, and if (as seems beyond doubt, from the work of Cannon and other investigators) it is the predominating one when the reaction is alkaline on one side and acid on the other, then the problem resolves itself into the reaction prevailing in the duodenum being the controlling element in the pyloric mechanism and the reaction on the gastric side being of secondary importance. This hypothesis finds some substantiation in the recent experiments of Foster and Lambert,[22] who were unable to hasten evacuation of the stomach by increasing the gastric acidity without altering the chemical reaction in the duodenum. Cannon, however, was able to delay evacuation by decreasing the acidity of solid food introduced into the stomach.

As the observations from which the foregoing conclusions have been drawn were made entirely with the use of liquids, it may be that the behavior of the pylorus toward liquids is different from its behavior toward solids. Cannon believes this to be the case and presents as a possible explanation the view that liquids do not excite the pyloric tonus that is manifested when solid food is ingested. It appears from the evidence presented above, however, that liquids of acid reaction and those inducing a secretion of considerable amounts of hydrochloric acid do excite pyloric tonus. Moreover, several clinical facts suggest the same behavior toward solid food, in diseased conditions, as have been described above for liquids. One of these is the relative frequency with which cases

22. Foster and Lambert: Jour. Exper. Med., 1908, x, 820.

of simple anacidity or achylia gastrica, without malignancy, are associated with rapid emptying of the stomach and persistent diarrhea only to be controlled by correcting the gastric secretory deficiency; and not less frequently are observed cases of hyperacidity with delayed emptying of the stomach, improving when the hyperacidity is reduced.

With the hope of observing the motor behavior of the stomach toward liquids, especially water, a cystoscope was kindly introduced by Dr. B. A. Thomas through the fistulous opening in my patient when the stomach was filled with water; but nothing more than the intermittent opening of the pylorus could be observed. It has recently been asserted by Cohnheim[23] and others that when water is swallowed, instead of entering the fundus, as solids do, it enters a small gutter formed by a horse-shoe-shaped band of muscle along the lesser curvature of the stomach, running from the cardia to the pylorus. He maintains that, even when the stomach contains food-masses, water does not come into contact with these, but, running through this gutter-like channel, passes immediately into the duodenum. This view is scarcely in harmony with the observations of the stimulating action of water on the flow of gastric juice, and no such formation as has been described could be seen in my patient by means of a cystoscope. It must be granted, however, that in this instance water did not enter at the cardia, as in normal individuals. Cohnheim's claim is somewhat substantiated by the anatomic investigations of Kaufmann,[24] who describes this horseshoe-shaped bundle of muscle running from the cardia to the pylorus.

This leads us to consider for a moment the motor functions of the stomach and the arrangement of foodstuffs when taken into it. Though Grützner[25] has shown the fallacy of the old idea of a general admixture of all food taken into the stomach, his views have, as yet, received little general recognition. Among the more recent workers to substantiate Grützner's claim is Prym.[26] The investigations of these two experimenters were carried on by feeding animals with foods of different consistency or different color, killing them at various periods of gastric digestion, and immediately freezing or coagulating the stomach and its contents. According to their observations, in the fundus, the portion in which active acidification and peptonization occurs, there is a distinct layer-like arrangement of the food. In general, the first food taken assumes the outermost position; that is, next to the mucous membrane.

23. Cohnheim: München. med. Wchnschr., 1907, liv, 2581.
24. Kaufmann: Ztschr. f. Heilk., 1907, xxviii, 203.
25. Grützner: Arch. f. d. ges. Physiol. (Pflüger's), 1905, cvi, 463.
26. Prym: München. med. Wchnschr., 1908, lv, 57.

That subsequently taken lies nearer the center of the cavity. This holds true if all the food taken is of the same consistency, or if that first taken is the more fluid. If the more solid elements are taken first, and subsequently the more liquid, the wave-like motion of the fundal portion of the stomach-wall forces the solid particles more and more toward the center of the cavity; so that eventually the more fluid portions of the contents assume the peripheral position. Only those portions in contact with the mucous surface of the stomach become acidified and peptonized. Those portions farthest from the mucous membrane remain totally unacidified for considerable periods of time.

In considering the motility of the stomach, the fundal and pyloric portions must be considered as quite distinct. From the time that the food enters the stomach, there is a gentle, wave-like motion, running from the cardia toward the pylorus. This extends to about two-thirds of the distance from the cardia to the pylorus, where the antrum pylori commences. This wave-like motion gradually sweeps the peripheral portion of the contents of the fundus, which have been acidified and liquefied, into the antrum pylori. At the beginning of the antrum pylori, the circular band of muscle becomes much thicker and, by its forcible contraction, practically divides the stomach cavity into two distinct chambers, the antrum pylori and the fundus. The antrum pylori, consisting of the pyloric third of the stomach, exhibits, instead of this almost continuous wave-like action of the fundal portion, an intermittent, extremely forcible contraction, which forces its acidified contents into the duodenum when the pylorus relaxes.

It is interesting in connection with these newer observations to note the following remarks which were written by Wilson Philip[27] almost a century ago and have apparently entirely escaped the attention of recent writers:

> When the foregoing experiment is considered it will appear, either that the food last received into the stomach is never mixed with that already there, and which has more or less undergone the action of the gastric fluid, or if they be mixed together, that the stomach has the power of again separating them, retaining the one and propelling the other into the intestine. These facts induced me to make some experiments on a large scale, for the purpose of ascertaining with great accuracy the process which takes place in the stomach, without which it is impossible to understand the nature of the symptoms which arise from its defects.
>
> With this view I examined the stomachs of about a hundred and thirty rabbits immediately after they had been killed in the usual way, which is by a blow on the back part of the head, at various periods of digestion. The following were the results:

27. Philip, A. W. Wilson: A treatise on indigestion, Edition 2, Philadelphia, 1822, p. 31.

The first thing that strikes the eye on examining the stomachs of rabbits which have lately eaten is, that the new is never mixed with the old food. The former is always found in the center, surrounded on all sides by the old food, except that on the upper part between the new food and the smaller curvature of the stomach there is sometimes little or no food. If, as we ascertained by more than twenty trials, the old and the new food be of different kinds, and the animal killed before a great length of time has elapsed after taking the latter, the line of separation is perfectly evident, so that the old may be removed without disturbing the new food. To ascertain this point we fed rabbits on oats, and after making them fast for sixteen or seventeen hours, allowed them to eat as much cabbage as they choose, and killed them at different periods, from one to eight hours, after they had eaten it.

On opening the stomachs of rabbits three or four weeks old, who both sucked and ate green food, we always found the curdled milk unmixed with the green food. Before the stomach was opened we could, from its transparency, see where the green food and where the milk lay.

If the old and the new food be of the same kind, and the animal be allowed to live for a considerable time after taking the latter, the gastric fluid passing from the old to the new food and changing, as it pervades it, renders the line of separation indistinct. So that on a cursory view we should suppose the old and the new food mixed together, but toward the small curvature of the stomach and still more toward the center of the new food, we find it, unless it has been very long in the stomach, undisturbed and comparatively fresh. All around, the nearer the food lies to the surface of the stomach the more it is digested. This is true even with regard to the food in the small curvature, compared with that nearer the center, and the food which touches the surface of the stomach is more digested than any other found in the same part of the stomach; but, unless the animal has not eaten for a great length of time, the food in contact with the surface of the stomach is in very different stages of digestion in different parts of this organ. It is least digested in the small curvature, more in the large end, and still more in the middle of the great curvature.

The foregoing observations apply to the cardiac portion of the stomach; the food in the pyloric portion is always found in a state very different from that just described. It is more equally digested, the central parts differing less from those which lie near the surface of the stomach. It is evident, however, that all the change effected in the stomach is not completed when the food enters this portion of it, because we find it more digested the nearer it approaches the pylorus, where, being ready to pass into the intestine, it has undergone all that part of digestion which is performed in the stomach.

It appears that in proportion as the food is digested it is moved along the great curvature, where the change in it is rendered more perfect, to the pyloric portion. Thus the layer of food lying next the surface of the stomach is first digested, and in proportion as this undergoes the proper change, is moved on by the muscular action of the stomach, that next in turn succeeds to undergo the same change. As the gastric fluid, to a certain extent, pervades the contents of the stomach, though apparently in no other way than by simple juxtaposition, for the arrangements of the food, above described, we never found disturbed; the change in each part, which in its turn comes in contact with the stomach, is far advanced before it is in actual contact with it; and consequently is soon after this in a proper state to be moved on toward the pyloric end.

Thus a continual motion is going on, that part of the food which lies next to the surface of the stomach passing toward the pylorus, and the more central parts approaching the surface; whether food is ever so digested in the small curvature as to be sent to the pyloric portion without having traversed the large curvature, I have not been able to ascertain. When rabbits have fasted sixteen or eighteen

hours, the whole food found in the cardiac portion, which is in small quantity compared to what is found in it after a fast of short duration, seems to be all nearly in the same stage with that next the surface of the large curvature, the gastric fluid having pervaded and acted on the whole, and is consequently, as far as we can judge, prepared to be sent to the pyloric end. . . .

Although the food is in the most digested state in the pyloric end, it appears from the fact just mentioned, and several other circumstances, that the change is chiefly effected in the great end of the stomach. . . .

From all that has been said it appears that the process which the food undergoes in the stomach is that of being formed into a mass in appearance nearly hemogeneous; that this process takes place only on or near the surface of the stomach, and that, in proportion as the food there situated undergoes the necessary change, it is by muscular power of the stomach moved onward toward the pylorus, making room for that which next succeeds until the whole contents of the stomach have undergone this process, the digested contents being regularly discharged into the duodenum, as they arrive at the pylorus, till most, and in some animals all the contents of the stomach are thus removed into that intestine; from which, after they have for some time been detained there, and mixed with bile and pancreatic fluid, they are continually passing into the adjoining parts of the canal.

If there are varying degrees of admixture of food and gastric juice in the different layers of the stomach-contents, and if the pyloric portion of the stomach-cavity contains only the well acidified and peptonized portions of the ingested material, it would be expected that the different portions of the stomach-contents would reveal varying degrees of acidity and peptic activity. Investigations have proved this to be correct. Sick,[28] by means of a stomach-tube, the lower end of which could be opened at will, found that the acidity of the fundal and pyloric portions of the gastric contents differed at different periods of gastric digestion. Shortly after food is taken, the acidity of the fundal contents is the greater; later in the process of digestion the acidity of the pyloric region exceeds that of the fundus.

More recently Landerer[29] has shown similar conditions to exist in the peptic activity of the fundal and pyloric contents. At first, that of the fundus is the greater; later, that of the pylorus becomes the greater.

Taussig and Rush[30] have studied the bearing that this separation of the fundal and pyloric portions of the stomach has on the interpretation of a test meal. They found that the amount of gastric contents obtained when the patient was in the sitting posture was usually much less than that obtained when the patient was first in a sitting position, then lying on the back, and finally lying on the right side. In the two latter postures they obtained from 17 to 65 c.c. more than could be obtained in the sitting posture. Finally, by introducing a known quan-

28. Sick: Deutsch. Arch. f. klin. Med., lxxxviii, 169.
29. Landerer: Deutsch. Arch. f. klin. Med., 1908, xciii, 563.
30. Taussig and Rush: Boston Med. and Surg. Jour., 1908, clviii, 79.

tity of water, they recovered from 11 to 64 c.c. of contents that could not be recovered by any of the former procedures. In studying the acidity of the first two portions removed from a series of 28 cases after an Ewald test breakfast Taussig and Rush found them to be approximately equal in eleven instances. The first portion was decidedly more acid than the second in fourteen instances, the reverse being true in three instances. In one case a difference of more than 50 in the total acidity of the two portions was observed. Taussig and Rush believe that their observations destroy, to a great extent, the value of the results obtained by the administration of a test meal. I think that they take too unfavorable a view of the subject. In the vast majority of subjects, by manipulating the stomach-tube, a certain amount of nausea can be produced; and, as this induces a tendency to vomit, the reversed peristalsis incident to this act will cause a fairly uniform admixture of all portions of the stomach-contents.

It has long been known that in various circumstances the regurgitation of bile and pancreatic juice into the stomach occurs. Beaumont noticed that the introduction of oil into the stomach of his patient caused the appearance of this phenomenon. It is only recently, however, that the constancy of this regurgitation under definite conditions has been well established. Boldyreff[31] observed that in dogs the introduction of oil or of any strongly acid solution regularly induced a regurgitation of bile, pancreatic juice, and succus entericus from the duodenum into the stomach, and that the same phenomenon occurred occasionally when the stomach had been empty of food for a considerable period of time and no oil or acid was introduced.

Investigating the frequency of this phenomenon in man, Volhard[32] was able to demonstrate the presence of trypsin in the stomach after an oil test meal in 86 per cent. of the cases studied. Faubel,[33] in a similar investigation, obtained a positive result in but 70.6 per cent. of his cases. He thinks it probable that this low percentage can be accounted for by a technical inaccuracy in his trypsin estimations. Lewinski[34] had positive results in practically the same percentage of cases as did Faubel. When, however, he neutralized the gastric acidity before the introduction of the oil trypsin was found in all the cases. More recently, Molnar[35] observed regurgitation of the duodenal secretions after the introduction of oil into the stomach in 48 out of 50 cases. The two patients in

31. Boldyreff: Arch. f. d. ges. Physiol. (Pflüger's), 1907, cxxi, 13.
32. Volhard: München. med. Wchnschr., 1907, liv, 403.
33. Faubel: Beitr. z. chem. Physiol. u. Path. (Hofmeister's), 1907, x, 35.
34. Lewinski: Deutsch. med. Wchnschr., 1908, xxxiv, 1582.
35. Molnar: Ztschr. f. klin. Med., 1909, lxvii, 189.

whom it did not occur suffered with carcinoma of the pylorus. If this constancy of the phenomenon is substantiated it may prove to be of no little value in the diagnosis of obstructions of the pancreatic and common bile ducts; and it is not impossible that future elaborations may make it of assistance in the diagnosis of functional derangements of the pancreas and liver.

SUMMARY.

Summarizing the results of the experiments and observations that have appeared in the literature and those that I have conducted, we may say that the importance of psychic stimuli in the production of gastric juice as determined by Pawlow and others in animals applies equally well to man. These psychic stimuli may be conveniently classified as positive and negative. Positive psychic stimuli are those which induce a flow of gastric juice. Negative psychic stimuli (if so paradoxical an expression be permissible) are those which inhibit or annul a gastric secretion. Psychic stimuli, both positive and negative, may originate in the higher mental processes as memory and imagination or, as is more usual, they may come from without and influence gastric secretion by appealing to any one of the five senses. Those stimuli which influence gastric secretion by appealing to the senses of taste or smell may be called direct psychic stimuli; those that act through the other senses or originate in higher mental processes may be called indirect or associated psychic stimuli. This dependence of gastric secretion on psychical processes and stimuli permits the formulation of the statement that appetite is the emotional expression of the group of phenomena of which the secretion of gastric juice is the physical expression.

The mechanical act of chewing seems to be powerless to induce a secretion of gastric juice; if the act of chewing becomes mentally associated with the process of eating agreeable food it probably is capable of inducing a flow of gastric juice.

The human stomach appears to behave in the same way toward chemical stimuli as does the dog's stomach. Water is a definite though not a powerful stimulus to gastric secretion. Hydrochloric acid is not a stimulus to gastric secretion. Egg-albumin does not induce the secretion of any more gastric juice than does an equal amount of water. The same is true of tea and commercial preparations of pepsin. Beef extracts are powerful stimuli to the secretion of gastric juice.

Bitter stomachics, though of themselves incapable of inducing a secretion of gastric juice, when administered previous to a substance which does induce a secretion of gastric juice, are capable of increasing this secretion. They may, in other words, be looked on as sensitizers of

gastric secretion. This sensitizing action is manifested when the stomachic is introduced directly into the stomach or when it merely remains for a time in the mouth and pharynx. Its action seems to be more powerful in the latter case than in the former.

It appears probable from the observations I have made on the effect of the introduction of acid and alkaline solutions into the stomach that the predominating influence in the control of the periodic opening of the pylorus is exerted by the chemical reaction of the contents on the duodenal side of the pylorus. Though the chemical reaction prevailing on the gastric side of the pylorus is of importance in the pyloric mechanism, it is distinctly subordinate to that on the duodenal side. This hypothesis explains the slow discharge of gastric contents of high acidity and the more rapid discharge of gastric contents of low acidity.

As observed by Wilson Philip almost a century ago, and as more recently determined by Grützner, Prym and others, the food in the stomach of the lower animals undergoes a layer-like arrangement: the liquid food and the solid food first introduced take a peripheral position, next to the mucosa, while that introduced later takes a more central position. As the portion next to the mucosa is peptonized and liquefied it is swept by the wave-like motion of the fundal wall into the antrum pylori preparatory to being ejected into the duodenum, when the next layer in the fundus comes into contact with the mucosa to be subjected to the same process. Though it has been impossible to repeat these observations in man, the same phenomena in all probability occur in the human stomach.

The regurgitation of bile and pancreatic juice from the duodenum into the stomach after the introduction of oil into the empty stomach seems to occur with great constancy in normal individuals. If future observations show this to be correct the phenomenon may prove to be of great clinical assistance in the diagnosis of affections of the pancreas and liver and of their excretory ducts in particular.

1218 Locust Street.

THE ABSENCE OF ADRENALIN IN MALIGNANT RENAL HYPERNEPHROMAS *

JAMES R. GREER, M.D., AND H. GIDEON WELLS, M.D.
CHICAGO

In view of the rather extensive discussion as to the origin of the so-called malignant hypernephromas of the kidney, it is strange that practically no attempt seems to have been made to determine whether adrenalin-like substances are present in these tumors. Investigation of most of the literature on hypernephromas fails to show any instances in which the presence of blood-pressure-raising substances has been sought, although a few authors call attention to the existence of a marked arteriosclerosis in patients dying of hypernephroma, and suggest that this arteriosclerosis may be the result of a flooding of the blood with excessive quantities of adrenalin. A case of this kind is described by F. J. Hall,[1] in which a patient, aged 56, with a hypernephroma of long duration, showed a most extensive calcareous infiltration of the arteries throughout the body. On the other hand, von Hansemann[2] reports that he could find no evidence of arteriosclerosis in fatal cases investigated by him. The only experimental evidence brought forward to show the presence of adrenalin in hypernephromas is the observation by Fedoroff,[3] that the extract of a hypernephroma caused dilatation of the pupil of the isolated eye of the frog, which is a most delicate test for adrenalin. He did not try the effect of this extract on blood-pressure or make any other tests for adrenalin.

On the other hand, our own observations on two specimens of malignant renal hypernephroma, one of which was kindly furnished by Dr. F. R. Zeit, the other by Dr. J. W. Jobling, gave entirely negative results.

FIRST TUMOR

Preparation of the Extract.—The tumor was carefully removed from the connective tissue capsule and other non-tumor tissue, thoroughly crushed, mixed with three times its wet weight of distilled water and allowed to extract with repeated agitations for six hours. This extract

---

* From the Laboratories of Physiology and Pathology of the University of Chicago.

1. Hall, F. J.: Hypernephroma, THE ARCHIVES INT. MED., 1908, ii, 355.
2. Von Hansemann: Ztschr. f. Krebsforsch., 1906, iv, 570.
3. Federoff: Folia Urol., 1908, ii, 551.

was very slightly acidulated and boiled to remove the protein. The coagulable protein was then filtered off, sufficient sodium chlorid added to make the filtrate of 0.9 per cent. strength, and the filtrate rendered sterile by boiling. As a control for this method of procedure the fresh adrenal glands of a normal dog were extracted in exactly the same way. Before using this latter extract it was diluted to one in ten, so that as far as the amount of the substance extracted is concerned the tumor extract should be two and one-half times as strong per equal volume.

These extracts were tested for adrenalin in three ways, as follows:

1. Effect on the Blood-Pressure of Two Normal Dogs.—Tracing 1 is the result obtained on the first dog tried. The animal was in good condition and was kept under light but constant anesthesia. The different solutions were injected intravenously as indicated in the tracing. It is to be noted that in every case the intravenous injection of the tumor extract produced a very slight rise, followed by a marked fall in the blood-pressure. This preliminary rise is no more than is caused by an equal amount of physiologic salt solution, as is shown by the tracing. The fall in the blood-pressure is similar to that produced by extracts of all organs except the adrenal and the hypophysis. For a control of this experiment, injections of different-sized doses of adrenalin chlorid were used. It will be noted that the injection of 1 c.c. of a 1 to 30,000 solution produced a striking rise in the blood-pressure, when compared with the slight initial rise after the injection of the tumor extract or of the salt solution.

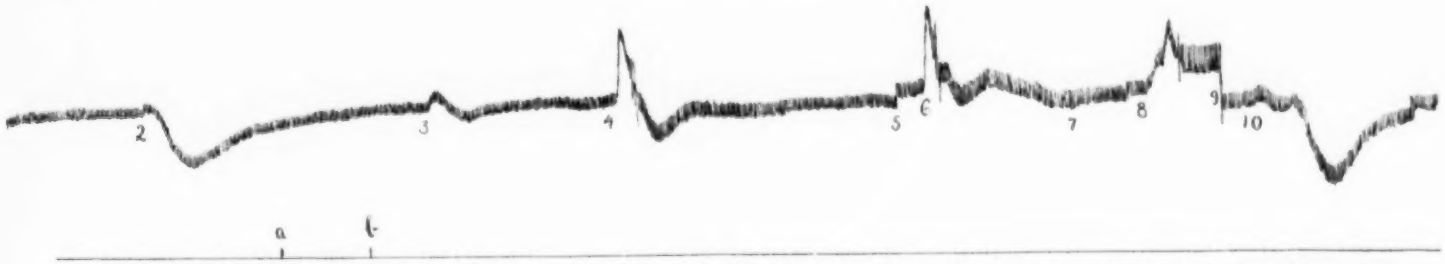
Tracing 2 was taken on another dog, using the same tumor extract as in the first dog, but instead of using adrenalin chlorid as a control the adrenal gland extract referred to above was used. In this case 50 c.c. of the tumor extract were injected at one time. This is noted at 9 (Tracing 2). This caused a marked fall in blood-pressure without any initial rise. As a control for this experiment 0.5 c.c. of the extract of the adrenal gland were injected (11, Tracing 2). This produced a marked rise in the blood-pressure, typical of adrenalin. It can be seen from the size of the dose of the tumor extract and of adrenal extract that the dose of the former was relatively two hundred and fifty times as large as the latter.

2. The Frog's Eye Test.—This test was described by Ehrmann,[4] who appears to be the first to apply and describe this test. It depends on the property of adrenalin to stimulate the plain musculature that is innervated by the sympathetic nervous system. The test consists of taking the enucleated eye of the frog and placing it in the solution to be tested. In

4. Ehrmann: Arch. f. exper. Path. u. Pharm., 1905, liii, 97.

Tracing. 1.—March 11, 1909. Weight of dog, 12 kilos. Blood-pressure from the carotid artery. Intravenous injections into the femoral vein. Time tracing in seconds. Index to tracing: 1. Injection of 5 c.c. tumor extract. 2. Injection of 10 c.c. tumor extract. 3. Injection of 15 c.c. tumor extract. 4. Injection of 15 c.c. 0.9 per cent. NaCl sol. 5. Injection of 5 c.c. 1/30000 adrenalin chlor. 6. Injection of 2 c.c. 1/30000 adrenalin chlor. 7. Injection of 1 c.c. 1/30000 adrenalin chlor.

Tracing 2.—Blood-pressure from carotid artery. Intravenous injection into the femoral vein. Time in seconds. Index to tracing: 9. Injection of 50 c.c. of tumor extract. 11. Injection of 0.5 c.c. of adrenal gland extract.



Tracing 3.—Blood-pressure from carotid artery. Intravenous injection into the femoral vein. Index to tracing: a—b, one minute time. 2. Injection of 30 c.c. tumor extract. 3. Injection of 30 c.c. 0.9 per cent. NaCl. sol. 4. Injection of 3 c.c. adrenal gland ext. 5. Drum stopped. 6. Injection of 3 c.c. adrenal gland ext. 7. Drum stopped. 8. Injection of 5 c.c. 1/50000 adren. chlor. sol. 9. Drum stopped. 10. Slow injection of 50 c.c. tumor extract.

the presence of very small quantities of adrenalin the eye of the frog shows marked dilatation. Ehrmann asserts that by this test adrenalin can be detected in a dilution as high as 1/10,000,000. Several tests were made of the tumor extract according to this method. A record of one of these tests is as follows:

Substance Tested.	Dilatation of Eye.	Time Required for Effect.
Adren. Cl. 1/50000	Complete.	10 minutes.
Adren. Cl. 1/100000	Complete.	18 minutes.
Adren. Cl. 1/500000	Complete.	60 minutes.
NaCl. (0.9%)	No dilatation.	Up to four hours.
Tumor extract.	No dilatation.	Up to four hours.
Adrenal gland extract.	Complete.	30 minutes.

It will be noted that this test was entirely negative; in fact, the size of the pupils placed in the tumor extract actually decreased.

3. The Colorimetric Test.—A rather delicate chemical test for the presence of adrenalin is the colorimetric one first described and applied by Comessatti.[5] This test is made by adding to the solutions to be tested equal amounts of a solution of mercuric chlorid. In the presence of adrenalin the solution turns pink, the depth of the hue depending on the amount of adrenalin. This test does not appear to be as delicate, however, as that with the frog's eye, for we could not get a positive reaction in a dilution of 1/500,000 of adrenalin chlorid, a strength of which is easily detected by the eye test. By this test the tumor extract gave entirely negative results, while the adrenal gland extract gave a strongly positive reaction.

SECOND TUMOR

This tumor was received fresh and was treated in exactly the same way as the other tumor, with this one exception, namely, that it was extracted for twelve hours, as against six for the former. For control of this extract another adrenal gland extract was prepared in exactly the same way as the tumor extract. This gland extract was also diluted to 1 in 10 as in the former case.

Tracing 3 gives the results of the injection of these extracts on the blood-pressure in a dog. In this case on the injection of 30 c.c. of the tumor extract there was a slight initial rise in the blood-pressure followed by a marked fall. Here again the initial rise caused by the tumor extract is no more than that produced by the same amount of salt solution. An injection of 3 c.c. of the adrenal gland extract produced a very marked rise in the blood-pressure. This is shown at 4 and 6 in Tracing

5. Comessatti: München. med. Wchnschr., 1908, lv, 1926.

3. This tracing also shows the effect of a dose of 5 c.c. of 1/50,000 adrenalin chlorid and of 50 c.c. of the tumor extract (8 and 10).

Frankel[6] has recently described the extreme delicacy of the test for adrenalin with the uterus of the rabbit. He asserts that when immersed in solutions containing as little adrenalin as 1 part in 10 to 20,000,000 the uterus will go into tetanus. This tumor extract was tested in this way, but instead of showing the presence of adrenalin by going into the typical tetanus, the uterus quickly lost completely its irritability.

The tests with the frog's eye and with the mercuric chlorid were entirely negative in repeated attempts.

GENERAL CONSIDERATIONS

The absence of the blood-pressure-raising principle of the adrenal from these tumors does not, however, indicate that they are not derived from adrenal rests in the kidney. This active principle of the adrenal is the product of the medullary portion of the gland, which is quite distinct from the cortex, functionally, embryologically and anatomically. Hypernephromas reproduce the cortical portion of the adrenal, which is derived from the same embryonal anlage as the kidney and the ovary, which structurally resembles quite closely the corpus luteum, and which functionally seem to have nothing to do with blood-pressure, but rather to be related to the generative functions.[7] The medulla of the adrenal, which secretes the active principle, is derived from the sympathetic nervous system, and, with possibly a few exceptions,[8] is not represented in hypernephromas. Therefore, the presence of adrenalin is not to be expected in hypernephromas, since the adrenal cortex, which these tumors reproduce, does not normally form adrenalin. It is possible that tumors arising from the adrenal itself may be found to contain adrenalin; indeed, Fölger[9] claims to have obtained a rise of blood-pressure in animals by injecting extracts of adrenal tumors of horses, but in this case the question may be raised as to whether the adrenalin was produced by the tumor or by the remnants of the adrenal.

6. Frankel: Arch. f. exper. Path. u. Pharm., 1909, lx, 395.
7. See Bullock and Sequeira: Tr. Path. Soc., London, 1905, lvi, 189. Thumim: Berl. klin. Wchnschr., Jan. 18, 1909, xlvi, 103.
8. See Ohlmacher, Jour. Med. Research, 1902, vii, 421.
9. Fölger: Monatschr. f. prakt. Tierheilk, 1908, xx, No. 4.

FURTHER OBSERVATIONS ON THE THIRD HEART SOUND *

WILLIAM SYDNEY THAYER, M.D.
BALTIMORE

At the last meeting of the Association of American Physicians[1] I made a few remarks concerning the frequency, especially in young people, of a third heart sound heard in early diastole somewhere between one-tenth and two and one-tenth of a second after the second sound of the heart, causing a characteristic protodiastolic gallop. This sound is especially common in the recumbent and left lateral postures and is more frequent in young individuals. It was pointed out that it was often associated with a palpable and sometimes even with a visible impulse, and this impulse was shown to be identical with the normal early diastolic elevation of the apex cardiogram. Further analogies were pointed out between this sound and that which characterizes the early diastolic gallop rhythm heard under various pathological conditions, especially in aortic insufficiency, in mitral stenosis and in adherent pericardium. Cardiograms and jugular tracings showed that the ascending limb of the protodiastolic elevation of the cardiogram corresponds with the descending limb of the *v* wave of the jugular pulse, but when allowance is made for transmission time the apex of the protodiastolic elevation falls often on a slight rise described first by Hirschfelder as the *h* wave; this wave was present or indicated in a surprising proportion of my cases.

During the past six months Dr. Peabody and I have endeavored to accumulate records of different forms of pathological gallop rhythm as well as of these instances of third sound in normal individuals with the view, if possible, of determining, first, the frequency of this phenomenon in the healthy man, and, second, its relation, if any, to the pathological protodiastolic gallop rhythm. While I am not ready at the present moment to enter into an extended discussion of the pathological gallop rhythms, there are certain points with regard to our observations which seem to me worth bringing up to-day.

---

* Read before the Association of American Physicians in May, 1909.

1. Thayer, W. S.: The early diastolic heart sound (the so-called third heart sound). Boston Med. and Surg. Jour., 1908, clviii, 713; Tr. Assn. Am. Phys., 1908, xxiii, 326.

I. THE FREQUENCY OF A THIRD SOUND IN NORMAL INDIVIDUALS AND THE CONDITIONS UNDER WHICH IT IS OBSERVED

We have studied a limited number of healthy patients who had entered the hospital for trivial surgical complaints, a number of normal boys and girls of different schools, as well as a series of physically healthy individuals at the city jail.[2] These observations have been in some respects rather surprising. I have examined altogether 231 consecutive individuals; in 65 per cent. of these subjects under the age of forty the third heart sound was present. This sound, however, is rarely audible in the erect posture; it is present commonly in the dorsal decubitus and is almost always clearer in the left lateral position, where the apex impulse is more evident. Its frequency varies in an interesting manner according to the age of the individual. The frequency with which the third sound was heard in these 231 individuals when arranged according to decades is shown by the accompanying table and chart (Fig. 1).

TABLE SHOWING THE FREQUENCY OF THE THIRD HEART SOUND IN TWO HUNDRED AND THIRTY-ONE NORMAL INDIVIDUALS

Decades	1	2	3	4	5	6
Cases	39	90	55	26	14	7
Percentage of cases with third sound	58.9	84.4	50.9	42.3	14	0

It may then safely be asserted that the early diastolic or third sound is a normal phenomenon in a large proportion of young individuals.

A further analysis of these cases shows that in every decade except the fifth, in which there were but 14 cases, the average pulse rate was somewhat slower among the cases in which the third sound was audible than among those in which it was not heard.

Cardiographic and jugular tracings have been taken in a number of cases. In all instances these show a rather marked protodiastolic elevation on the cardiogram. They do not, however, show as constant an *h* wave as was indicated in my early tracings.

It may then safely be asserted that the early diastolic or third sound is a normal phenomenon in a large proportion of young individuals.

II. WHAT IS THE CAUSE OF THIS PHENOMENON?

While these observations do not justify positive conclusions on this point, they have on the whole strengthened me in the feeling that was expressed last year that the sound is probably the result of a sudden tension of the mitral valve occurring with the first inrush of blood at the

2. For the privilege of examining these prisoners I am indebted to the courtesy and kindness of Dr. G. L. Wilkins.

beginning of diastole. As has been previously shown, this sound is unquestionably coincident with the impulse associated with the first inrush of blood from auricle to ventricle; it is especially frequent in cases in which this impulse is unusually marked.

One might, therefore, expect the sound to be audible in normal individuals:

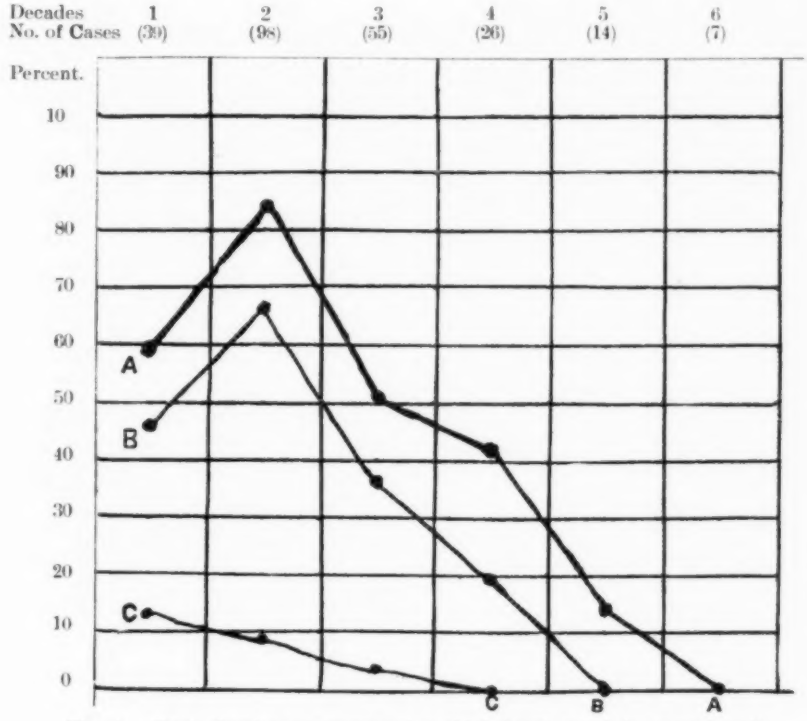


Fig. 1.—Chart showing occurrence of a third heart sound in normal individuals. The uppermost line (A-A) indicates percentage of cases in which the sound was heard; the second (B-B) line, the percentage of cases in which the sound was heard in the dorsal decubitus; the lowest line (C-C), the percentage of cases in which the sound was heard in the erect posture.

1. In positions in which the apex is especially accessible.

2. Under circumstances in which the quantity of blood in the left auricle is large.

But when we consider the conditions under which the sound is heard in normal individuals we find that it is best audible:

1. In positions in which the apex is especially accessible—i. e., on the back and left side.

2. With a rather slow pulse, which means a larger volume of blood.

3. During the first slow beats of expiration where, beside the influence of rate, we have the presence of more blood as a result of the increased aspiration into the lung during inspiration.

Fig. 2.—Third heart sound (protodiastolic gallop). Normal heart. The upper tracing is from the jugular vein; the middle tracing is the apex cardiogram; the lowest tracing is from the brachial artery. The timer registers tenths of seconds.

Moreover, in pathological conditions one might expect the diastolic impulse and sound to be more marked:

(a) In conditions in which the quantity of blood entering the ventricle in diastole is exceptionally large.

(b) Where the filling of the ventricle is unusually rapid.

(c) Where the ventricle, owing to changes in the walls or a diminished vascular tonus, is unusually distensible or dilated.

Now (a) the conditions under which an increased quantity of blood enters the ventricle in diastole are especially aortic and mitral insuffi-

ciency. In the former condition the third sound is present in most cases.

With regard to mitral insufficiency I have been struck this winter by the frequency with which a slight dull sound is heard in early diastole, especially in those cases in which the heart's action is slow. Figures 4 to 6 show the marked protodiastolic impulse in cases of gallop rhythm in aortic and mitral insufficiency.

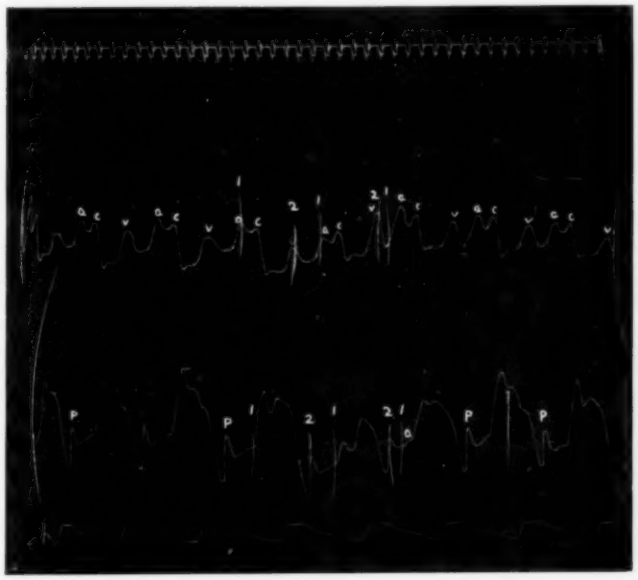


Figure 3.—Third sound (protodiastolic gallop). Normal heart. The uppermost tracing is from the jugular vein; the middle tracing is the apex cardiogram; the lowest tracing is from the brachial artery.

Adherent pericardium (b) is *the* striking example of a condition in which the filling of the ventricle might be expected to be especially rapid; but here the early diastolic sound and shock are characteristic.

With regard to conditions (c) in which the tonicity of the ventricle is low and the walls might be easily distensible, as in patients after acute infections, it may be said that a diastolic gallop is generally regarded as common under these circumstances. I can not say that I have been as much struck with its frequency here as under some other circumstances, but it may well be that its absence in hospital cases in which the patients

have been long in the recumbent posture is due to the fact that a large amount of venous blood has accumulated in the splanchnic vessels.

In cases of dilatation of the left ventricle, which are commonly associated also with a relative mitral insufficiency, the condition is, as is well known, especially common. In all these conditions, with the presence of gallop rhythm, the protodiastolic elevation on the cardiogram is marked.

With regard to mitral stenosis, in which, as is well known, a third sound is very common, the condition is not always analogous. In some

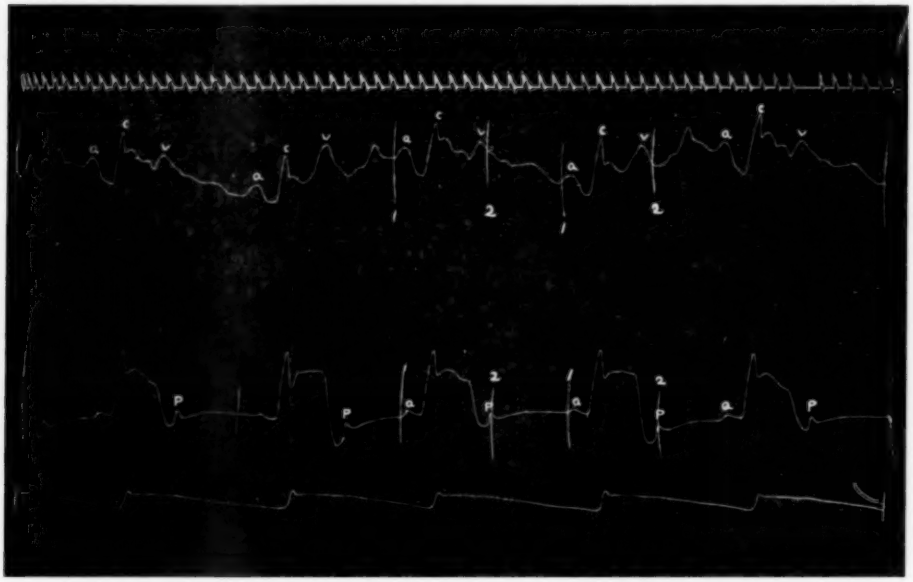


Figure 4.—Protodiastolic gallop rhythm. Mitral insufficiency. The uppermost tracing is from the jugular vein; the middle tracing is the apex cardiogram; the lowest tracing is from the brachial artery.

cases associated with insufficiency, in which the stenosis is not of high degree, the conditions, as has been pointed out, are such that similar manifestations might be expected, and this is the case. In others an opening snap, occurring apparently rather early, is audible without a definite protodiastolic shock. In cases of extreme stenosis it is possible that the tension of the valves giving rise to the sound may occur as a result of pressure from above in association with the diastolic relaxation of the ventricle, as was suggested by Potain. With this exception, however, it seems highly probable that the normal and pathological early dias-

tolic sounds are due to a similar phenomenon, at least in the great majority of cases. This is borne out by the similar character of the sounds and their relation to the cardiogram and the jugular pulse.

III. WHY IS IT THAT THE SOUND IS SO MUCH BETTER HEARD IN THE RECUMBENT POSTURE AND ON THE LEFT SIDE?

Is it simply because of the greater accessibility of the apex? This seems to me hardly possible. If, however, we adopt the working hypothe-

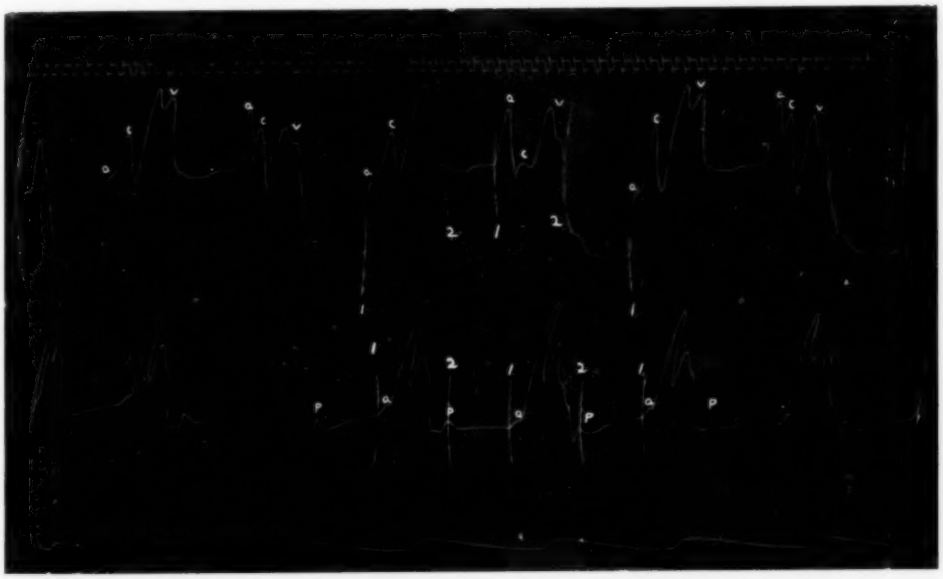


Figure 5.—Protodiastolic gallop rhythm. Mitral insufficiency. The uppermost tracing is from the jugular vein; the middle tracing is the apex cardiogram; the lowest tracing is from the brachial artery.

sis that the sound is due to a sudden early diastolic tension of the mitral valve its greater frequency in the recumbent posture might easily be explained by the increased quantity of blood which must reach the left heart in this position owing to the more favorable conditions for venous flow. In connection with this question I have the distinct impression that the sound is more marked in individuals who have been in the erect posture and who lie down for the examination than in those who have been longer in the recumbent posture. In these cases the venous flow to the heart may well be increased on the first change of position owing to

the elevation of the extremities, an increase which, after a time, might disappear as a result of the accumulation of blood in the abdominal vessels. In a few cases I have compared the heart sounds of patients in the dorsal decubitus with those heard when the legs and arms were held by attendants in an elevated position. The elevation of the extremities has seemed to me distinctly to increase the intensity of the sound.

Figure 6.—Protodiastolic gallop rhythm. Mitral and aortic insufficiency. The uppermost tracing is from the jugular vein; the middle tracing is the apex cardiogram; the lowest tracing is from the brachial artery.

IV. WHY SHOULD THE SOUND BE MORE MARKED IN THE LEFT LATERAL POSTURE?

The answer to this would seem to be simple enough. The slight and almost constant difference between the frequency with which the sound is heard in this position and in the dorsal decubitus may well be accounted for by the greater accessibility of the apex and by the fact that the entrance of blood into the ventricle does not in this position take place against gravity.

In addition to this it may be that the apex systolic murmur so commonly heard in young individuals in the recumbent and especially in the

left lateral posture, in perfectly normal hearts, may represent, in some instances, a slight functional mitral insufficiency, in which case the greater frequency of the sound in these positions would be easily explicable.

In conclusion, these observations would seem to justify the following assertions:

1. The third heart sound is present in the majority of young individuals in the recumbent and left lateral posture.

2. This sound may well be due, as first suggested by Hirschfelder and later, independently, by Gibson and myself, to the sudden tension of the auriculoventricular valves as a result of the first rush of blood from auricle into ventricle in diastole.

3. Pathologically, the sound is especially frequent in conditions in which the quantity of blood entering the ventricle from the auricle is especially large; in which the diastole is unusually rapid; in which there is a lowered ventricular tonus or dilatation of the ventricle. The most striking examples of these conditions are aortic and mitral insufficiency, some instances of slight mitral stenosis combined with insufficiency, adherent pericardium, myocardial weakness and dilatation of the ventricle.

4. A protodiastolic gallop, therefore, is not *per se* a pathological manifestation.

406 Cathedral Street.

THE EFFECT OF TUBERCULOSIS ON THE HEART*

F. M. POTTENGER, A.M., M.D., LL.D.

MONROVIA, CAL.

A good heart is one of the best assets possessed by a patient suffering from pulmonary tuberculosis. From the earliest infection by the tubercle bacillus it is more or less disturbed in its action, and as the focus of infection grows larger the effect on the heart becomes greater. The deleterious influences which react on the heart are many and from varied sources. The heart problem increases in complexity as well as in importance as the disease advances in severity. While it would seem that, with the present-day knowledge of tuberculosis and the means at our command for making an early diagnosis, we should see a greatly diminished number of cases of advanced tuberculosis in the future, yet I fear that it will be a long time before tuberculosis will be generally diagnosed early; and I do not doubt that any knowledge that may be added bearing on the condition of the heart in advanced infections will be welcome and of clinical value.

There are many difficulties in the way of giving an opinion on the condition of the heart in individuals suffering from tuberculosis, especially those suffering from advanced tuberculosis. The position of the heart in the chest is altered, the pulmonary circulation is embarrassed, changes occur in the systemic arteries as well as the heart itself, blood pressure is altered, the relative intensity of the heart tones is changed, numerous murmurs appear at the various valve areas and numerable adventitious sounds are heard. Without bearing these facts in mind many erroneous opinions will be given.

The first change that occurs in the heart and circulatory system is noted as soon as the infection is of sufficient grade to cause clinical symptoms. This is an acceleration of the pulse. It is probably of toxic origin and is associated with a lowering of the blood pressure due to the action of the tubercle toxins on the vasodilators. This quickening of the pulse may be slight, in which case it would perhaps be noted only after exertion; or it may be marked and even show when the patient is at rest. The causes which operate to quicken the pulse during the course of pulmonary tuberculosis are many. The rapidity is in

*Read before the Sixteenth International Medical Congress, Budapest, Hungary, Aug. 29 to Sept. 4, 1909.

part doubtless a physiological response on the part of the heart to compensate for the lowering of the blood pressure caused by the dilatation of the arterioles; in part due to a lack of power on the part of the heart muscle itself, resulting from the action of toxins or because of overwork; in part due to a stimulation of the sympathetic fibers in the chest, and doubtless in part due to the interference with the inhibitory action of the vagus.

As the disease progresses and the action of the toxins becomes more manifest, general muscular wasting occurs in which the heart muscle bears its share. Then it is that we find the greatest changes in the blood pressure. Opposing the fall in pressure we find, early in the disease, hypertrophic changes in the right ventricle; and later, quite often, a thickening of the arterial walls.

Having noticed a thickening of the arterial walls in many cases of advanced tuberculosis, I decided to find out how general it is, with the result as noted in Table 1. In the first place, I found it most commonly in patients who had suffered from the disease for many years, consequently in those in whom the fibroid form of the disease predominated. I do not doubt that the cause is the prolonged action of weak toxins on the vessel walls. This opinion is supported by Table 1, which shows the comparative frequency of palpable arteries in those ill less than one year, from one to two years and more than two years:

TABLE 1.—SHOWING THE COMPARATIVE NUMBER OF PALPABLE RADIALS IN PATIENTS WHO HAVE BEEN ILL LESS THAN ONE YEAR, FROM ONE TO TWO, AND MORE THAN TWO YEARS. TOTAL NUMBER OF PATIENTS, 162

	Duration of Disease.		
Condition of Radials.	Less Than 1 Year.	1 to 2 Years.	More Than 2 Years.
Palpable	14	20	60
Non-palpable	14	21	33

I took as an index to the condition of the arterial walls the condition of the radials, and determined whether or not they were palpable either after stripping the vessel from below upward with the second finger of one hand and from above downward with the second finger of the other hand and then using the first finger to do the palpating of the empty vessel, or by palpating the vessel while the blood was shut off from the artery by the cuff of the blood pressure apparatus. Very inexact data will be obtained unless the column of blood is first expressed from the artery.

Analyzing the blood pressures[1] of the 162 cases here represented, we see that there were 11 first-stage cases with an average pressure of systolic

1. Stanton's sphygmomanometer was used in making the blood-pressure observations recorded in this report. The average blood pressure of 20 healthy adults taken under the same conditions showed systolic 130, diastolic 110.

108, diastolic 78; 21 second-stage cases with an average pressure of systolic 108, diastolic 81, and 130 third-stage cases with an average of systolic 103, diastolic 75. It must be remembered that these pressures were taken in Southern California, where climatic conditions favor a relatively low pressure. If we note the influence exerted by the palpable arteries (we include only the 130 cases in Stage III), we shall see that the average pressure in the 83 cases in which the arteries were palpable was: systolic 105, diastolic 76; while that of the 47 cases where they were not palpable was: systolic 102, diastolic 75. That this condition of the arteries is not influenced largely by the age of the patients is very evident from Table 2, for of those who had palpable arteries none were between the ages of 15 and 20; 21 between 20 and 30; 45 between 30 and 40; 20 between 40 and 50, and 7 between 50 and 65. And of those whose arteries were not palpable 11 were between the ages of 15 and 20; 35 between 20 and 30; 16 between 30 and 40; 6 between 40 and 50, and 1 between 50 and 65.

TABLE 2.—CONDITION OF THE ARTERIES ACCORDING TO AGE

Conditions of Arteries.	15 to 20 Years.	20 to 30 Years.	30 to 40 Years.	40 to 50 Years.	50 to 65 Years.
Radials Palpable	00	21	45	20	7
Radials not Palpable....	11	35	16	6	1

Now, if we note the effect exerted by myocarditis (in this class I placed only those who showed marked clinical signs), we shall note the opposite effect. The average pressure in the 62 cases in the third stage showing myocardial change was: systolic 97, diastolic 70; while the average pressure in the 68 which did not show this change was: systolic 110, diastolic 82.

Further analysis of these cases seems to indicate that these two factors, thickening of the arterial walls and degeneration of the heart muscle, are two very potent factors in modifying the blood pressure in tuberculous patients. Table 3 shows this very plainly for the cases which did not show myocarditis. Where myocarditis was not present, those patients who had palpable radials had a blood pressure of, systolic 113, diastolic 82, even higher than the pressure of the first- and second-stage cases. In those of the same class whose radials were not palpable the blood pressure was, systolic 105, diastolic 83, making a difference of about 8 points in the systolic pressure, which seems to be due to the condition of the arteries as determined by the radials. This difference, although present, is not apparent in the cases showing myocardial change as arranged in Table 3. If Table 4 is studied, however, it will be seen that the reason for those who have palpable radials and myocarditis having a lower blood pressure than those whose radials did not show

the change is that several of the former had such severe myocardial change that the tendency to raise the pressure owing to the changes in the arteries was overcome and the actual pressure was lowered. This might indicate also that this thickening of the arteries, while helping to maintain the blood pressure in an earlier stage of advanced tuberculosis, finally proves detrimental in that it causes too great a strain to be thrown on the heart, and the heart muscle, being unable to meet the demand, fails.

TABLE 3.—SHOWING THE EFFECT OF THE CONDITION OF THE ARTERIAL WALLS ON BLOOD PRESSURE WHEN ASSOCIATED WITH AND WITHOUT MYOCARDIAL CHANGE

		Myocarditis			Non-Myocarditis	
Radials.	No. Cases.	Systolic	Diastolic	No. Cases.	Systolic	Diastolic
Radials Palpable ...	41	97	70	42	113	82
Radials Non-palpable	21	97	69	26	105	83

Myocardial change is present in some degree in practically all cases of tuberculosis. In the earlier stages of the disease when the patient's general condition is good, this change is a hypertrophy of the right ventricle to enable it to do the extra work forced upon it by the diminution of the pulmonary vascular area. Later, through the action of toxins, the general malnutrition, overwork and other deleterious agencies, the muscle degenerates and weakens. The field of cardiac response becomes diminished and whereas, at first, the heart is able to perform its function by calling on its reserve energy and working at its maximum power as evidenced by the hypertrophy which takes place, it is now no longer able to do so, and as a result the circulation is carried on imperfectly and dyspnea and cyanosis appear.

In determining the presence of myocardial change, I took into consideration both clinical symptoms and signs on the part of the heart itself; and designated as cases of myocarditis only such hearts as showed marked change.

There are many difficulties in the way of giving an opinion on the heart in advanced tuberculosis. In the first place, we do not have the same anatomical relations in advanced tuberculosis as we do in the normal chest. Through the effect of pleurisies, contractions and compensatory emphysemas the heart is often displaced and the heart valves no longer bear their normal relation to the superficial landmarks. If the heart is uncovered by the retraction of a portion of the lung, sounds that are not at all intensified may appear much louder than they would under normal conditions, and, on the other hand, if a large portion of emphysematous lung be interposed between the heart and chest wall the sounds will appear much weaker than they really would with normal covering, and it would be very difficult to accurately judge their intensity.

The presence of infiltrations and cavities also alter the quality and apparent intensity of the sounds. It can readily be seen, then, that it is difficult to compare and determine the relative intensity of the sounds at the different valve areas.

In making the observations recorded here I was compelled to disregard entirely the usual location of the valve sounds on the surface of the chest because the hearts were displaced to one or the other side in many instances. My data on the various valves was taken at the point where it seemed that the valve in question would most probably be located when the shifting of the heart had been considered.

The following observations were made with the stethoscope:

Apex—
- **Weak, 7 times.**
- **Strong, 5 times.**
- **Double, 89 times.**
- **Gallop rhythm, 17 times.**
- **Bruit, organic 6, functional 11 times.**
- **Triple sound, 1.**
- **Irregular, 2.**

Aortic—
- **First sound weak, 21 times.**
- **Second sound accentuated, 72 times.**
- **Second sound weak, 5 times.**
- **Bruit, systolic 6; diastolic, 4; organic, 5; functional, 5.**

Pulmonic—
- **First weak, 18 times.**
- **Second accentuated, 94 times.**
- **Second double, 35 times.**
- **Bruit, 6 times.**

Tricuspid—
- **Insufficiency, 4 times.**

Adventitious Sounds—
- **Probably pleuropericardial adhesions, 15 times.**
- **Pericarditis, 1 time.**
- **Pericarditis (adhesive) 3 times.**

Some of the observations mentioned above require explanation because the personal element always comes into play in characterizing observations of this kind. Errors of judgment are prone to creep in, but a few words of explanation will doubtless make the meaning clear.

A double beat was observed at the apex in 89 of the 162 patients. I designated as double what I considered as a departure from the normally recognized firm tone of the apex. The degree of doubling varied a great deal from what might be considered as a slight impurity to two very distinct sounds. It is estimated that a double sound at the apex is heard in about 10 per cent. of normal hearts, but it will be seen that in the patients here reported it occurred in more than 50 per cent. of the cases.

The frequency with which accentuation of the second aortic was found also requires explanation. In some cases this might be produced by the thickening of the systemic arteries; in others, it is only apparent and not actually an accentuation, the apparent accentuation depending on the nearness to infiltrations and cavities; in some cases it is due to the fact that the valve is uncovered and consequently seems louder and more accentuated than it is.

Three of the bruits designated as organic occurred in one family.

The four cases of tricuspid insufficiency were due to advanced stages of degeneration and dilatation of the heart muscle.

During the course of this investigation my attention was called to the Bock stethoscope as offering help in determining the relative intensity of the heart sounds. I regret that I did not have the Bock record in all instances, but I have tried it in a sufficient number of cases to demonstrate its value. By studying Table 4 it will be seen that the Bock readings give a fair estimation of the condition of the heart muscle. In interpreting the Bock readings it must be remembered that the standard is an arbitrary one and the readings of each heart must be considered alone. Bock has determined that for the normal individual the aortic sound should be about one-third less than that heard at the apex, and the pulmonary sound from five to fifteen points below the aortic.

Another very important topic for consideration in discussing the heart in its relation to advanced tuberculosis is the effect produced on it by the displacement which occurs on account of the changes in the lung and pleura. That this has received too little consideration in the past is self-evident.

It is natural to suppose that organs perform their functions best when in their natural positions. The heart in its normal position lies on the diaphragm and swings from the great vessels which serve as points of fixation at the base. It is surrounded and limited in its motion by the pericardium, and the amount of motion allowed the heart is dependent, to a certain extent, on the size of the pericardium. The pericardium is fixed at five points: to the under surface of the sternum, to the diaphragm, to the right and left pleuræ and to the great vessels of the chest. The heart is allowed slight motion within the pericardium under normal circumstances, as is noted on the change of position from lying on one side to lying on the other. Changes of this character in no wise interfere with the heart in the performance of its function because the position and size of the pericardium is not changed, the large vessels are lying free and easy in their normal place and no impediment is offered to the free and natural movements of the heart itself or to the

TABLE 4.—EFFECT OF TUBERCULOSIS ON THE HEART

Sex.	Stage; Turban.	Age.	Duration of Illness, Yrs.	Involvement.†	Blood Pressure.		Radials.*	Position of Heart.			Heart Tones.							Bock.		
					Systolic.	Diastolic.		Fourth Interspace. R. Cm.	Fourth Interspace. L. Cm.	Diameter.	Mitral.	Aortic.	Pulmonic.	Tricuspid.	Adventitious Sounds.	Heart Muscle.	Remarks.	Apex.	Aortic.	Pulmonic.
F.	I.	26	3	R. > L.	115	82	—	3.75	6.25	10	1st double.							85	62	62
F.	"	18	1½	L. > R.	115	84	—	3.5	4.5	8	Slight gallop rhythm.							82	75	80
M.	"	32	1½	L. > R.	100	74	+	3.0	7.0	10		2d accent.	2d accent.							
M.	"	18	5½	R. > L.	95	65	—	3.0	6.25	9.25		2d accent	2d accent.							
F.	"	30	½	L. > R.	110	72	—	2.25	6.75	9		Systolic murmur organic.								
M.	"	26	2½	L. > R.	125	100	—	3.75	8.0	11.75										
M.	"	13	1	L. > R.	88	55	—	2.5	5.5	8.0										
M.	"	21	3	L. > R.	132	74	—	3.75	7.0	10.75										
F.	"	22	13	R. > L.	98	70	—	2.75	7.0	9.75								80	55	55
M.	"	29	¼	L. > R.	124	100	+	3.25	10.5	13.75		2d accent						80	70	65
F.	"	34	1	L. > R.	112	77	—	4.0	7.0	11.0								72	60	64
M.	II.	24	2	L. > R.	96	69	—	4.0	7.87	11.87								70	55	65
M.	"	31	7	R. > L.	130	96	+	3.75	5.5	9.25		2d accent.	1st weak.					65	55	35
M.	"	30	⅓	L. > R.	113	80	+	3.75	7.0	10.75								85	70	65
F.	"	29	3	L. > R.	114	76	—	2.75	8.0	10.75	Double.							85	75	70
M.	"	22	1/12	R. > L.	108	88	—	3.5	7.0	10.5	Systolic bruit (functional).		2d accent.					90	72	70
M.	"	21	1/6	L. > R.	120	86	—	3.0	8.0	11.0	Systolic bruit (functional).		Systolic bruit (functional).					75	60	67
F.	"	17	½	R. > L.	112	83	—	3.5	5.75	9.25										
F.	"	14	½	R. > L.	98	69	—	4.5	4.25	8.75	Systolic bruit (functional).		2d accent.		Pleuropericardial adhesions.					

* In this column + stands for "palpable;" — for "non-palpable."
† R. > L. signifies right lung involvement greater than left; L. > R., left lung involvement greater than right.

M.	II	32	5/6	R. > L.	114	94	—	2.75	7.5	10.25	.....	.....	2d sl. accent...								
F.	"	25	5/12	L. > R.	92	67	—	3.0	5.5	8.5	1st double.....										
M.	"	23	1	L. > R.	109	78	—	2.0	9.25	11.25	.....	.....									
M.	"	32	1½	R. > L.	136	98	+	3.0	7.25	10.25	Systolic murmur (org).	1st weak.....	1st weak.								
M.	"	50	4	L. > R.	100	68	+	3.25	7.75	11.0	1st double.....	2d accent double.	2d accent.								
F.	"	20	1	R. > L.	110	83	—	3.5	8.5	12.0	Double murmur; systolic and diastolic (organic.)	Double murmur (org'ic).	.....	.....	.....	.....	.....	82	80	80
M.	"	29	1	L. > R.	98	67	+	3.25	8.0	11.25	1st double.....	2d sl. accent...									
M.	"	51	1	R. > L.	118	98	+	4.0	6.0	10.0	1st double.....	2d accent (metallic).									
M.	"	38	4	R. > L.	85	60	—	4.5	6.75	11.25	Double.....	2d accent.....	2d accent.....	.....	Pleuropericardial adhesions.	.....	Pericarditis.				
M.	"	30	½	R. > L.	88	65	—	5.0	7.5	12.5	Double.....	Systolic bruit (functional).	2d sl. accent...	.....	.....	.....	.....	88	80	82
F.	"	49	4	L. > R.	140	122	—	3.25	7.75	11.0	Double, irregular.	.....	Bruit; 2d accent.	.....	.....	.....	.....	80	75	85
M.	"	39	1	R. > L.	120	104	—	3.75	6.75	10.5	1st double.....	.....	.....	.....	.....	.....	.....	95	90	80
F.	"	20	6	L. > R.	122	98	+	3.5	7.0	10.5	1st double.....	.....	2d sl. accent; double.	.....	.....	.....	.....	80	70	75
M.	III.	25	1	L. > R.	116	80	—	3.0	8.5	11.5	1st double bruit functional; gallop rhythm.	.....	2d accent.	.....	.....	Myocarditis.	.....			
F.	"	25	1½	R. > L.	108	83	—	3.0	7.25	10.25	Double.....	.....	Bruit.								
M.	"	31	1	L. > R.	82	57	+	4.75	8.5	13.25	Double; gallop rhythm.	1st weak; 2d accent.	1st weak; 2d accent.	.....	.....	Myocarditis.	.....			
F.	"	27	1¼	L. > R.	100	75	—	6.0	8.5	14.5	1st weak; gallop rhythm.	1st weak.....	2d sl. accent...	.....	.....	Myocarditis.	.....	75	60	75
M.	"	52	2	L. > R.	100	76	—	1.5	8.5	10.0	1st double.....	2d sl. accent...	2d accent double.	.....	.....	.....	.....			
F.	"	19	2	L. > R.	94	68	—	4.0	8.0	12.0	1st double.....	2d accent.....	2d accent.....	.....	.....	.....	.....	75	70	92
F.	"	40	9	L. > R.	90	68	+	−2	12.0	10.0	1st double.....	1st } 2d } weak	1st weak.....	Insufficiency.	Pleuropericardial adhesions.	Myocarditis.	.....	70	65	75
F.	"	41	7	L. > R.	96	74	—	4.0	7.25	11.25	Systolic bruit functional.	1st weak; 2d accent	2d accent.....	.....	.....	Slight myocarditis.	.....			
F.	"	23	2½	R. > L.	110	83	—	3.5	6.0	9.5	Triple sounds.	.....	2d accent.....							

TABLE 4.—EFFECT OF TUBERCULOSIS ON THE HEART (Continued)

Sex.	Stage; Turban.	Age.	Duration of Illness, Yrs.	Involvement.	Blood Pressure.		Radials.	Position of Heart.			Heart Tones.							Bock.		
					Systolic.	Diastolic.		Fourth Interspace.		Diameter.	Mitral.	Aortic.	Pulmonic.	Tricuspid.	Adventitious Sounds.	Heart Muscle.	Remarks.	Apex.	Aortic.	Pulmonic.
								R. Cm.	L. Cm.											
F.	III	36	2	L. > R.	90	68	+	2.75	8.0	10.75	1st double	1st weak; 2d accent.	1st weak; 2d accent.			Myocarditis.				
F.	"	47	9	R. > L.	95	56	−	4.0	6.5	10.5		2d accent	2d accent					85	75	65
M.	"	32	1	L. > R.	108	76	+	2.75	10.0	12.75	1st double	2d accent	2d accent metallic.					75	65	45
F.	"	37	4	L. > R.	100	70	+	3.75	3.75	12.5	1st double		2d double.		Pleuropericardial adhesions.	Myocarditis.		92	70	75
M.	"	38	4	L. > R.	98	72	+	2.75	8.0	10.75	Double		2d double accent.			Myocarditis.		65	63	70
M.	"	30	2	R. > L.	108	76	+	5.0	4.5	9.5	1st double	2d accent	2d accent					83	75	77
F.	"	36	2	R. > L.	115	78	−	4.5	6.5	11.0	1st double	2d sl. accent.						80	75	75
M.	"	24	1½	L. > R.	88	54	+	3.5	8.0	11.5	1st double	2d accent	1st weak.			Myocarditis.		67	50	30
M.	"	36	½	L. > R.	122	88	+	3.75	5.75	9.5		2d accent	2d accent					65	70	55
F.	"	39	2	L. > R.	87	68	+	1.5	11.0	12.5	Double	1st weak	1st weak.			Myocarditis.				
F.	"	36	2	L. > R.	116	88	−	0.5	8.5	9.0	1st double	2d accent	2d accent					80	70	70
M.	"	34	1	R. > L.	100	72	+	6.5	7.75	14.25	1st weak	1st very weak.	1st very weak.			Myocarditis.				
F.	"	29	4	R. > L.	80	58	−	5.25	4.25	9.5	Double	2d double accent.		Insufficiency.		Myocarditis.				
F.	"	34	1½	L. > R.	100	75	+	2.0	9.0	11.0	Gallop rhythm.	2d sl. accent.	2d accent			Myocarditis.				
M.	"	29	⅔	R. > L.	122	86	+	3.75	7.5	11.25	Bruit systolic; organic.	2d metallic accent.					Nephritis.	80	75	72
F.	"	30	½	L. > R.	95	77	+	2.25	6.75	9.0	1st double; systolic murmur (functional).	Systolic murmur (functional).								
M.	"	20	7/12	L. > R.	104	74	−	4.0	6.75	10.75	1st double					Myocarditis.				
M.	"	37	2	R. > L.	106	80	+	4.5	5.5	10.0	1st double	1st weak; 2d weak.	2d double.			Myocarditis.		82	72	60

M.	III	36	11/12	R. > L.	98	70	+	4.0	8.5	12.5	1st double.....	1st weak.....	1st weak; 2d dbl. accent.	.....	.....	My ocardi-tis.	.....	86	65	67
F.	"	43	4	R. > L.	90	67	+	5.0	6.5	11.5	1st weak; gal-lop rhythm.	1st weak; 2d weak.	.....	.....	.....	My ocardi-tis.	.....	65	45	35
F.	"	28	13	R. > L.	102	70	+	3.0	7.0	10.0	Systolic bruit (functional).	.....	Systolic bruit (functional).	.....	.....	.....	.....	82	65	65
F.	"	40	9	L. > R.	133	108	+	4.5	9.5	14.0	.....	.....	.....	.....	.....	.....	.....	90	75	65
M.	"	25	3	L. > R.	118	78	+	4.0	8.25	12.25	Double.....	Slight accent..	.....	.....	.....	.....	.....	85	65	75
M.	"	39	6	R. > L.	138	110	+	3.5	6.0	9.5	Double.....	Sl. accentuat-ed.	.....	.....	Pleuropericar-dial adhe-sions.	.....	.....	90	80	85
M.	"	45	3	L. > R.	104	80	+	3.75	9.0	13.75	Weak; 1st double.	1st weak; 2d accent.	1st weak; 2d accent.	.....	.....	My ocardi-tis.	Irregular.	90	65	70
M.	"	33	3½	L. > R.	94	66	+	3.0	10.5	13.5	1st double.....	2d accent.....	2d db. accent. systolic bruit.	.....	.....	.....	.....	95	70	70
M.	"	37	2	L. > R	118	88	+	3.75	9.0	12.75	.....	.....	.....	.....	.....	.....	.....	80	75	65
M.	"	38	19	L. > R.	135	85	+	2.5	8.0	10.5	Strong,duoble.	2d weak.....	2d double accent.							
M.	"	28	½	L. > R.	114	80	+	4.25	6.5	10.75	Weak.....	.....	2d sl. accent...							
M.	"	29	1½	L. > R.	100	70	—	4.75	7.0	11.75	.....	.....	2d double.....							
M.	"	25	1½	L. > R.	108	78	—	1.5	9.0	10.5	.....	2d sl. accent..	2d markedly accent.							
F.	"	22	1½	R. > L.	110	80	—	2.75	5.5	8.25	1st double....	.....	2d accent double.							
M.	"	38	9	L. > R.	122	90	+	2.5	7.0	9.5	.....	Systolic bruit.								
F.	"	47	¾	L. > R.	80	58	+	1.0	7.75	8.75	1st double gal-lop rhythm.	2d sl. accent...	2d sl. accent...	.....	.....	My ocardi-tis.				
F.	"	27	4½	L. > R.	122	90	—	—5.5	+11.5	6.0	.....	2d accent.....	3d dbl. mark-edly accent.							
M.	"	41	2	R. > L.	108	78	+	3.25	6.75	10.0	1st double.....	2d metallic ac-cent.	2d double met-allic accent.							
M.	"	21	⅜	R. > L.	108	78	—	.....	.....	.....	1st double.....	2d double.....	2d double met-allic accent.	.....	.....	My ocardi-tis.				
M.	"	21	¼	L. > R.	110	80	—	2.0	8.0	10.0	1st double.....	.....	2d double ac-cent.	.....	.....	My ocardi-tis.				
M.	"	36	2½	L. > R.	90	72	+	2.0	12.75	14.75	Strong double.	1st weak.....	1st weak; 2d sl. accent.	.....	.....	My ocardi-tis.				
F.	"	43	15	L. > R.	112	84	+	—3.5	19.0	15.5	Strong.....	2d accent.....	2d accent double.							
F.	"	18	⅓	L. > R.	82	58	—	0.5	8.0	8.5	.....	.....	2d metallic sl. accent.							
M.	"	31	4	R. > L.	120	90	—	3.75	8.5	12.25	.....	2d accent.....	1st weak; 2d accent.	.....	.....	Sl. myocar-ditis.				
M.	"	46	4½	L. > R.	105	67	+	0.75	10.5	11.25	.....									

TABLE 4.—EFFECT OF TUBERCULOSIS ON THE HEART (Continued)

Sex.	Stage; Turban.	Age.	Duration of Illness.	Involvement.	Blood Pressure.		Radials.	Position of Heart.			Heart Tones.							Back.		
								Fourth Interspace.												
					Systolic	Diastolic		R. Cm.	L. Cm.	Diameter	Mitral.	Aortic.	Pulmonic.	Tric spid.	Adventitious Sounds.	Heart Muscle.	Remarks.	Apex.	Aortic.	Pulmonic.
M.	III	50	10	L. > R.	88	55	+	2.5	8.5	11.0	Weak; 1st double.	2d sl. accent.	2d double metallic.	Systolic bruit.	.....	Myocarditis.				
F.	"	25	1	R. > L.	112	80	—	2.5	6.0	8.5	1st double.....									
F.	"	40	3	L. > R.	85	63	—	2.0	10.0	12.0	Gallop rhythm.	Diastolic murmur (organic).	2d accent.....	.....	.....	Myocarditis.				
M.	"	26	2½	R. > L.	108	74	+	4.0	6.5	10.5	1st double.....	2d double accent.	2d accent.							
F.	"	35	1	L. > R.	96	66	+	3.75	8.75	12.5	1st double.....	2d accent.....								
M.	"	30	3	L. > R.	92	64	—	1.75	9.0	10.75	.....	.....	.....	Relative insufficiency.	.....	Myocarditis.	Adhesive pericarditis; nephritis.			
M.	"	15	1	L. > R.	94	69	—	2.0	7.25	9.25	1st double.....	2d accent metallic.	2d accent double.							
M.	"	63	4	R. > L.	95	75	+	2.0	8.0	10.0	1st double	2d accent metallic.	2d accent.							
F.	"	33	2	R. > L.	96	60	—	4.75	5.5	10.25	.....	.....	2d sl. accent..	.....	.....	Myocarditis.				
F.	"	44	2	R. > L.	98	58	+	2.0	7.5	9.5	1st double.....	2d accent.....	2d accent.....	.....	.....	Myocarditis.				
F.	"	36	4	L. > R.	92	62	+	3.5	6.5	10.0	Double.....	.....	2d double.....	.....	.....	Myocarditis.				
M.	"	29	¾	R. > L.	100	80	+	5.5	6.0	11.5	1st double.....	2d accent double.	2d accent double.	.....	.....	Myocarditis.				
M.	"	40	24	L. > R.	114	85	+	1.75	9.25	11.0	1st double.....	.....								
M.	"	65	9	R. > L.	135	100	+	0.0	12.5	12.5	.....	2d accent.....	2d accent.....	.....	.....	.....	Arteriosclerosis.			
M.	"	47	3	R. > L.	106	74	+	4.0	9.0	13.0	1st double....	1st weak; 2d double.	2d accent.							
M.	"	20	¼	L. > R.	100	70	—	4.0	7.0	11.0	1st double; gallop rhythm.	.....	.....	.....	Pleuropericardial adhesions.	Myocarditis.				
F.	"	38	7	R. > L.	106	72	+	0.75	10.5	11.25	.....	2d accent.....	2d accent.....	.....	.....	.....	Pericarditis.			
F.	"	38	1	L. > R.	92	56	—	0.75	8.75	9.5	1st double.....	2d accent.....	2d accent double.							

M.	III	31	2	L. > R.	98	54	+	0.0	9.0	9.0	1st double.....	2d accent.....	.....	.....	.....	My ocardi-tis.				
F.	"	25	4	R. > L.	95	73	—	3.5	6.25	9.75	1st double; systolic bruit functional.	.....	2d accent.....	.....	.....	My ocardi-tis.				
F.	"	28	2	L. > R.	130	105	+	0.0	8.5	8.5	1st double.....	2d sl. accent...	2d accent.							
M.	"	27	1½	L. > R.	94	56	+	0.0	10.5	10.5	.....	2d accent.....	2d accent.							
M.	"	32	3½	L. > R.	85	56	+	4.25	6.0	10.25	1st double.....	.....	.....	.....	.....	My ocardi-tis.				
M.	"	29	2	L. > R.	80	52	+	3.25	9.0	12.25	Gallop rhythm.	Sl. diastolic murmur (functional). 2d sl. accent.	2d accent double.	.....	.....	My ocardi-tis. My ocardi-tis.				
F.	"	48	1½	R. > L.	85	60	+	5.25	10.5	15.75	Systolic bruit (organic).	2d accent double.	2d accent double.	Insufficiency.	.....	My ocar i-tis.				
M.	"	49	4	L. > R.	108	86	+	2.5	8.25	10.75	1st double	2d accent.....	2d weak.....	.....	.....	My ocardi-tis.				
M.	"	33	5	L. > R.	128	95	—	4.25	7.5	11.75	.....	2d accent.....	2d accent double.	.....	.....	.....	Nephritis.			
F.	"	27	1	L. > R	95	72	—	—1.5	13.0	11.5	Double	Systolic murmur (func.).	2d accent.....	.....	.....	My ocardi-tis.	Nephritis.			
M.	"	38	3	L. > R.	100	75	+	—2	11.5	9.5	.....	2d accent double.	2d accent.....	.....	.....	My ocardi-tis.	Nephritis.			
M.	"	23	2	R. > L.	94	58	—	5.0	8.5	13.5	.....	2d accent metallic.	2d sl. accent..	.....	.....	My ocardi-tis.				
F.	"	16	1½	L. > R.	112	78	—	1.5	9.5	11.0	.....	.....	2d accent.....	.....	.....	My ocardi-tis.				
M.	'	37	4	L. < R.	108	84	+	3.5	8.0	11.5	.....	2d accent.....	.....	.....	.....	My ocardi-tis.				
M.	"	26	1½	R. > L.	110	62	+	2.0	8.5	10.5	1st double.....	2d accent.....	2d accent.....	.....						
M.	"	30	1	R. > L.	86	64	—	5.0	7.0	12.0	1st double; gallop rhythm.	1st weak; 2d double metallic.	1st weak; 2d accent.	.....	.....	My ocardi-tis.				
F.	"	34	4	L. > R.	114	68	+	4.5	6.5	11.0	Weak.....	Weak.....	Weak.....	.....	.....	My ocardi-tis.	Adhesive pericardits.			
F.	"	24	½	L. > R.	114	76	—	1.5	9.5	11.0	.....	.....	2d accent.....	.....	Pleuropericardial adhesions.					
F.	"	25	1	L. > R.	105	80	—	3.25	7.5	10.75	.....	.....	2d accent double.	.....	.....					
F.	"	33	1½	L. > R.	86	54	+	2.75	8.5	11.25	.....	.....	2d sl. accent..	.....	.....	My ocardi-tis.				
F.	"	15	2	L. > R.	88	60	—	1.5	10.0	11.5	Gallop rhythm.	Diastolic murmur; funct.	.....	.....	.....	My ocardi-tis.				
F.	"	30	10	R. > L.	98	62	+	3.75	6.0	9.75	Systolic murmur organic.	1st weak; 2d accent.	2d accent.....	.....	.....	.....	.....	70	50	

TABLE 4.—EFFECT OF TUBERCULOSIS ON THE HEART (Continued)

Sex.	Stage; Torban.	Age.	Duration of Illness. Yrs.	Involvement.	Blood Pressure.		Radials.	Position of Heart.			Heart Tones.							Bock.		
					Systolic.	Diastolic.		Fourth Interspace.		Diameter.	Mitral.	Aortic.	Pulmonic.	Tricuspid.	Adventitious Sounds.	Heart Muscle.	Remarks.	Apex.	Aortic.	Pulmonic.
								R. Cm.	L. Cm.											
M.	III	49	9	L. > R.	92	60	+	—1.5	12.0	10.5	1st double; 2d accent	2d double accent.	.....	.....	.....	My ocardi-tis.	Arterio-sclerosis.			
M.	"	36	18	L. > R.	92	60	+	1.0	12.0	13.0	1st double.....	1st accent metallic.	.....	.....	.....	My ocardi-tis.				
F.	"	41	2	R. > L.	105	82	+	4.0	6.0	10.0	.....	Systolic murmur (org.).	2d accent.							
M.	"	38	3	R. > L.	122	95	+	3.75	7.5	11.25	Systolic bruit (organic).	2d accent.....	2d accent.							
M.	"	32	¼	R. > L.	102	77	+	5.0	7.5	12.5	.....	.....	2d sl. accent.							
F.	"	33	1	R. > L.	96	64	—	5.0	7.0	12.0	Gallop rhythm.	1st weak; 2d accent.	2d double and accent.	.....	.....	My ocardi-tis.				
M.	"	41	1½	L. > R.	115	85	+	4.25	7.25	11.5	.....	2d accent.....	.....	.....	.....	.....	Nephritis.			
F.	"	40	1	L. > R.	110	74	+	1.0	10.0	11.0	1st double.....	2d accent.....	2d accent.							
F.	"	40	3	R. > L.	110	80	—	4.5	5.5	10.0	1st double.....									
M.	"	32	⅓	R. > L.	120	85	+	5.0	6.5	11.5	1st double.....	1st weak; 2d accent.	1st weak; 2d accent.	.....	Pleuropericardial adhesions.	My ocardi-tis, dilatation.	.....	82	70	75
M.	"	42	2	L. > R.	108	80	+	4.5	10.5	15 0	1st strong double.	.....	2d double.....	.....	.....	My ocardi-tis.	.....	85	40	50
M.	"	24	7	R. > L.	90	66	+	4.0	9.0	13 0	.....	.....	2d sl accent...	.....	.....	.....	.....	88	60	65
F.	"	31	7	L. > R.	97	68	—	2 75	7.75	10.5	1st double	.....	.....	.....	.....	.....	.....	77	75	75
F.	"	25	3	L. > R.	87	62	—	1.75	9 5	11 25	1st double gallop rhythm.	1st weak; 2d accent.	1st weak; 2d double.	.....	.....	My ocardi-tis.	.....	65	65	70
M.	"	33	4	R. > L.	108	78	+	4.5	7.5	12.0	1st double	2d metallic....	Systolic bruit; 2d double.	.....	.....	My ocardi-tis.	.....	70	62	55
F.	"	40	2	R. > L.	106	74	—	2.0	6.5	8.5	1st double.....	.....	.....	.....	.....	.....	.....	85	75	75
M.	"	37	1½	L. > R.	107	75	+	3.0	10.25	13.25	1st double gallop rhythm.	2d accent.....	1st weak; 2d dbl. accent.	.....	.....	My ocardi-tis, dilatation.	.....	75	65	65
M.	"	17	⅓	L. > R.	96	66	—	4.5	6.5	11.0	1st double.....	.....	1st weak; 2d accent.	.....	.....	.....	.....	77	75	75

M.	III	40	5	R. > L.	110	75	+	5.75	9.5	15.25	1st double		2d sl. accent			My ocardi-tis.		72	80	65
F.	"	21	5	L. > R.	93	67	—	3.75	10.75	14.5	1st double		2d accent double.		Pleuropericardial adhesions.	My ocardi-tis, dilat on.		77	87	75
F.	"	30	7	R. > L.	135	94	+	7.25	4.75	12.0	1st double gallop rhythm.		2d accent					77	60	55
M.	"	46	10	L. > R.	84	68	+	4.0	9.5	13.5	1st double	1st accent	1st accent.		Pleuropericardial adhesions.	My ocardi-tis.		85	77	80
M.	"	26	4	L. > R.	78	54	+	3.75	7.0	10.75	1st double		2d accent			My ocardi-tis.		75	70	70
M.	"	27	2	L. > R.	138	120	+	4.0	12.0	16.0	1st double	2d accent	2d accent		Pleuropericardial adhesions.	My ocardi-tis, dilatation.	Athlete	92	85	85
M.	"	25	1¼	R. > L.	102	84	—	5.25	9.0	14.25	1st double	2d accent	2d accent				Athlete	80	80	77
M.	"	35	15	R. > L.	122	96	+	5.5	8.5	14.0	1st double	2d accent	2d accent		Pleuropericardial adhesions			90	70	85
M.	"	26	2	R. > L.	120	102	+	5.5	9.0	14.5	1st double	2d accent	2d accent double.			Hypertrophy.	Athlete	87	70	80
M.	"	37	1	R. > L.	120	105	+	3.75	8.5	12.25	1st double							80	75	68
M.	"	22	2	R. > L.	112	95	—	4.5	10.0	14.5	1st double	2d accent	2d accent					85	80	80
M.	"	61	37	R. > L.	130	78	+	3.75	9.0	12.75	Systolic bruit (functional).	2d accent	2d accent		Pleuropericardial adhesions.		Arteriosclerosis.	92	88	70
M.	"	35	2	L. > R.	104	88	+	4.25	8.75	13.0	1st double irregular.	1st weak	1st weak; 2d dbl. accent.					75	62	75
M.	"	25	2	R. > L.	100	78	—	4.75	6.75	11.5	1st double		2d accent double.					80	67	70
F.	"	34	5	L. > R.	94	74	+	3.5	8.5	12.0	Gallop rhythm.		2d accent			My ocardi-tis.		75	75	87
M.	"	28	7	L. > R.	74	60	+	3.5	8.25	11.75	Bruit functional, double.	2d accent	2d accent		Pleuropericardial adhesions.	My ocardi-tis.		78	85	90
M.	"	22	2	L. > R.	122	98	+	4.5	9.0	13.5	Bruit functional.	2d accent	2d accent			Sl. myocarditis.		82	75	77
M.	"	32	4	L. > R.	120	95	+	2.75	10.0	12.75	1st double		2d accent		Pleuropericardial adhesions.			80	70	65
F.	"	45	3	L. > R.	112	85	—	2.25	10.0	12.25	Double	1st weak; 2d double.	sl. accent; 2d double.					80	65	85

outflow of blood in the vessels. When, owing to contraction of one or both lungs, traction is made on the pericardium through its attachments with the pleura, a very different condition is brought about and the heart is forced to work at a great disadvantage. This can be readily understood if we take an extreme case in which the heart has been drawn up and out until the apex is found in the left axilla owing to marked contraction of the left upper lobe and compensatory emphysema of the right lung. In such a case we must assume that the pericardial space is encroached upon, thus interfering with the free movements of the heart itself. The traction of the pericardium on the vessels not only changes them from their natural position, but bends them in their course and thus throws an extra amount of work on the heart. What is true in this extreme case is also true in those of less degree, but to a less extent. For the heart to perform its function under these difficulties would tax a heart muscle of normal power; but, in cases like these, the heart muscle is perhaps always the seat of degenerative change and consequently less able to meet the increased work thrown upon it.

In determining the deep cardiac dulness in order to estimate the size of the heart, I found considerable difficulty. In the first place, it is very difficult to percuss the deep borders with accuracy. The degree of error may be reduced to a minimum, however, by the employment of several different kinds of percussion to check each other. I used two or more of the following methods in each case: finger-finger percussion, Ebstein's percussion, rubber-tube percussion and auscultatory percussion.

There is some doubt as to what should be considered the normal limits of the normal heart. Of course, this differs according to the age and size of the individual and size and shape of the chest. Reiss[2] gives the following measurements from averages taken from a number of medium-sized individuals:

Distance of right border of heart from median line, third interspace, 2.75 cm.; fourth interspace, 3.75 cm.

Distance of left border of heart from median line, third interspace, 4.75 cm.; fourth interspace, 7.5 cm.

Sahli,[3] commenting on these measurements, says that they make the heart too small. If we take these measurements as a standard, however, it will be seen that a large percentage of the hearts in patients suffering from advanced tuberculosis are displaced. Of the 162 hearts examined, 58 were in practically the normal position, 27 were displaced to the right and 77 were displaced to the left. Of the Stage I cases one was displaced and 10 were in normal position. Of Stage II cases, 4 were

2. Reiss: Ztschr. f. klin. Med., 1888, xiv, 12.
3. Sahli: Diagnostic Methods, Philadelphia, 1905.

displaced and 17 were in normal position, and of Stage III cases, 99 were displaced and 31 were in normal position.

The question of the size of the heart has been one of great interest for many years. Of course, the measurements here given furnish no accurate data on this question because they are taken from patients in whom the disease has existed for some time and consequently are records of pathological hearts. Of the 162 hearts examined, 70 were under 11 cm. in diameter measured on a level with the fourth interspace, and 92 were more than 11 cm. Of course, it must be remembered that we are not always measuring the same cross-section of the heart, for in the displacement that occurs different portions of the heart are found on a line with the fourth interspace. It must also be understood that no effort was made to give the greatest cross-diameter of the heart in these measurements. It is very probable that these figures are somewhat in error as to the size of the heart, for signs of hypertrophy of the right ventricle were present in a large number of the cases, which, together with the traction of the pleura on the pericardium, as it often occurs in the advanced cases, would probably have a tendency in certain cases to force the heart backward. Thus a considerable degree of enlargement of the heart might be present without enlarging its borders as found on percussion. The same condition results from the fact that as the heart is pushed to the left it is forced to turn backward by the fact that the walls of the chest turn backward.

CONCLUSIONS

1. A relative low blood pressure is found in tuberculosis, especially in advanced tuberculosis.

2. The factors which favor low pressure are the effect of the toxins on the vasodilators, the weakness of the heart muscle and general wasting.

3. The factors which have a tendency to maintain pressure are hypertrophy of the heart muscle and thickening of the systemic arteries.

4. Thickening of the systemic arteries occurs perhaps as a result of the action of the toxins on the vessel wall and is found especially in patients who have had tuberculosis for some time.

5. Myocarditis is a condition very common in advanced tuberculosis and one which, if recognized, yields to appropriate treatment in many instances.

6. It is difficult to give an opinion on the heart tones in advanced tuberculosis because conditions surrounding the valves are changed by such things as infiltrations, cavities, emphysemas and contractions.

7. In the majority of advanced cases (99 out of 130) the heart is displaced and working at a disadvantage.

8. In estimating the size of the heart it must be remembered that as the heart pushes over to the left it pushes backward and consequently the lateral diameter as taken on a level with the fourth interspace does not give an adequate idea of the real or true size of the heart; also that the hypertrophy of the right heart often throws the left ventricle backward, producing the same result.

INFLUENZAL MENINGITIS *

DAVID J. DAVIS, M.D.

CHICAGO

While the question of the relation that Pfeiffer's bacillus bears to influenza or "grip" may be considered an open one, the pathogenicity of this organism is strikingly demonstrated by its occasional occurrence in pure growth in the meningeal exudate in cases of meningitis. Such a case, illustrating the fact that this organism at times may be highly pathogenic and presenting certain other interesting features, is here described.

REPORT OF CASE

The clinical history, furnished by Dr. F. Churchill and Dr. C. B. Reed, is as follows:

Patient.—Male child, one of twin brothers, each weighing 7 pounds, born Oct. 3, 1908. The mother had borne nine children and was in perfect health before the present delivery, which was normal and at full term. Other members of the family were also well. The baby was put to the breast eleven hours after birth, fed every three hours and did well until the morning of October 8, when the bowel movements were green and contained mucus and curds. The next day the child moaned constantly and on the 10th refused to nurse at 6 a. m. and was dull and drowsy during the day. On the 11th a "sinking spell" occurred in the morning and the patient became cold and cyanotic.

Examination.—At this time a physical examination was made by Drs. Churchill and Reed. The development and nutrition were good; color dusky. The baby was quiet and relaxed but appeared drowsy. The result of the examination of the head, chest, abdomen and limbs was negative. Rigidity was not present and no signs suggesting meningeal irritation appeared.

On October 12 the "sinking spells" continued and early in the morning general twitchings occurred, but no actual convulsions. They continued through the day, together with the marked cyanosis and comatose condition. Death occurred at 5 p. m. on the ninth day after birth and on the fourth day of the disease. The temperature from October 9 to October 12 ranged between 101.8 and 104.5 F.

The twin brother was healthy at birth and continued so until October 8, when he began to have numerous bowel movements, followed the next day by a continuous temperature. At noon, October 11, twitchings began which continued for seventeen hours. His condition grew gradually worse and death occurred on October 15, seven days after the onset. No autopsy.

Autopsy.—In the first case a postmortem examination was made seventeen hours after death.

Following is the anatomic diagnosis: Acute catarrhal gastroenteritis; acute purulent lepto-meningitis; acute parenchymatous, degeneration of the heart, liver and kidneys; acute swelling of the spleen, multiple ecchymoses of the pleura and thymus.

* From the Pathologic Laboratory of Rush Medical College, Chicago.

The body was very cyanotic and postmortem rigidity was not present. In the abdominal cavity a few drops of yellow fluid occurred but the peritoneal surfaces were smooth and glistening. No evidence of omphalitis. In the pericardium there were about 2 c.c. of clear fluid and the pleural cavities were free. On the surface of the thymus a few small ecchymoses, pin-head in size, occurred, and similar hemorrhages were found on the pleural surfaces. The lungs and bronchi were normal. The mucosa of the stomach and intestine was red throughout and in the ileum and large bowel were small hemorrhagic spots, pin-head in size. The myocardium, liver and kidneys showed acute degeneration; the adrenals, pancreas, gall bladder, urinary bladder and genital organs presented no noteworthy changes. The mesenteric lymph glands were soft and slightly enlarged.

Over the entire convex surface of the brain were well-defined areas of greenish-yellow, friable, purulent exudate, irregular in shape and from one to several sq. cm. in size and 1 to 5 mm. thick. Between these areas the meninges appeared smooth and transparent. At the base, especially in the region of the optic chiasm and the pons and along the larger blood vessels the deposit was more abundant and diffuse and from 1 to 5 mm. in thickness. The blood vessels everywhere were engorged and usually, especially at the base, surrounded by the abundant exudate. The ventricles were not dilated and the fluid was clear. In the spinal canal a large amount of turbid purulent exudate occurred about the cord. No pathological changes were present in the nasal sinuses or in the tympanic cavities.

Bacteriological Examination.—Meningeal Exudate: Inside and outside the polynuclear cells were enormous numbers of small Gram-negative polar staining bacilli. Some of the cells were packed with these bacilli, but none were found in the mononuclear or endothelial cells. Cultures on blood agar plates gave, in twenty-four hours, an abundant growth of small dewdrop-like colonies in every way characteristic of *Bacillus influenzæ*. One other colony, a staphylococcus and evidently a contamination, appeared on one of the plates, and about this was observed a cluster of larger influenza colonies indicating the symbiotic property characteristic of this organism. In the fluid obtained from the spinal canal the bacilli were likewise found in pure growth and in very large numbers.

Heart's Blood: In the heart's blood were found on culture a few colon bacilli. Repeated attempts to isolate influenza bacilli on pigeon blood agar failed. The pericardial fluid was sterile.

Peritoneal Fluid: In smears a few polymorphonuclear cells, many small mononuclear cells and a few Gram-negative polar staining small bacilli were found. Cultures on blood agar plates gave numerous typical influenza colonies. Three or four colonies of colon bacilli appeared on the plate also, and about them occurred the characteristic cluster of larger influenza colonies.

To summarize, in the meningeal exudate about the brain and spinal cord and in the peritoneal fluid were found influenza bacilli in large numbers and in pure growth. The few colon bacilli in the peritoneal fluid and heart's blood and the staphylococcus colony in the culture from the meningeal exudate were undoubtedly contaminations and may be disregarded.

Morphologically and culturally the bacilli isolated from this case corresponds to the typical influenza bacillus isolated from other sources. On media other than hemoglobin media no growth takes place and on pigeon-blood agar it grows profusely. The tendency to form threads, while evident, is not marked. Polar staining with methylene blue is distinct and dilute carbolfuchsin stains the bacillus uniformly.

Pathogenicity: A few drops of exudate obtained from the base of the brain were injected into the peritoneal cavity of a guinea-pig with no results. A second guinea-pig inoculated intraperitoneally with growth from two blood-agar slants died in thirty-six hours. Examination showed a purulent peritonitis and right salpingitis. In the peritoneal pus were many leucocytes and bacilli, some of the latter being intracellular and in cultures numerous influenza colonies appeared with a few colonies of *B. coli*. Pure growths of *B. influenzæ* were obtained from the heart's blood, pericardial fluid, both pleural fluids and the right Fallopian tube.

Two guinea-pigs, inoculated subdurally with a few drops of a dense suspension of the bacilli, died within twenty-four hours. The meninges in one were bloody but an exudate did not appear. The bacilli were recovered from the surface of the cortex and from the base of the brain, but from no other part of the body. In the second animal the meninges were congested but no exudate was evident. Bacilli were found in the meningeal fluid as in the first animal, but not in other parts of the body. Three guinea-pigs, inoculated with this organism behind the eyeball into the orbit, developed no symptoms other than a slight conjunctivitis. One of the animals, killed five days later, showed no evidence of meningitis or other lesions.

Microscopic Examination of Exudates and Tissue.—Cerebrospinal fluid: In the turbid fluid obtained at the base of the brain approximately 80 per cent. of the cells are polymorphonuclear leucocytes and the remainder mononuclear cells. The latter vary in size, many of them having large faintly staining nuclei with abundant protoplasm. Others are typical small mononuclear cells and are not numerous.

Meninges: Pieces of tissue including the meningeal exudate and the underlying cortex were removed from the region of the Sylvian fissure, the temporal lobe and the cerebellum, for microscopic examination. The exudate, especially about the blood vessels, is abundant and composed chiefly of polymorphonuclear and mononuclear cells. The relative proportion of these cells varies in different regions. Near the surface of the exudate the polynuclears may comprise 80 per cent. or more, while nearer the cortex the mononuclear cells increase in number. Here and there are large endothelial cells, which frequently show phagocytosis of from one to several polynuclear and mononuclear cells. About the blood vessels the exudate is intense, but no changes are observed in the intima or media of the arteries. Thrombi occur in some of the small veins and the thin walls in places are infiltrated with leucocytes. Some free blood is found here and there in the exudate outside the vessels. Very little fibrin is apparent in the formalin-fixed tissue. The cortex shows little change. Occasionally near the surface a polymorphonuclear cell or plasma cell is seen, but deeper no cellular infiltration appears. Changes in the blood vessels and hemorrhages are not present.

Peritoneal Fluid: This is slightly turbid and in suspension are a number of leucocytes, 80 per cent. of which are small mononuclear, and 20 per cent. polymorphonuclear cells. The bacilli are chiefly outside the leucocytes.

Intestines: Sections were made of the intestinal wall at different points. In one section the glands of the mucosa show some disintegration and between them are found a few polymorphonuclear cells and eosinophiles. The muscularis is normal and the blood vessels in the subserosa and in the mucosa are engorged. In other sections some congestion and cellular infiltration occur but no changes appear in the serosa.

The myocardium, lungs, kidneys, thymus, spleen, adrenals and lymph glands present no noteworthy changes. Sections of the liver show congestion of the small blood vessels and slight infiltration of round cells and leucocytes about some of the bile ducts.

GENERAL CONSIDERATIONS

It is unnecessary to review the literature on influenzal meningitis at this time since this has been thoroughly done recently by others. Adams,[1] in 1907, tabulated the cases and found 21 in which the influenza bacillus was isolated from the meningeal exudate in pure culture. Cohoe[2] this year finds, including his own, 24 cases and gives an analysis of the important features. In addition a considerable number of cases are reported in the literature in which a mixed infection of influenza bacilli with, as a rule, Gram-positive diplococci occurred. In such cases it is impossible to say how important the influenza bacilli were in causing the lesion. It should be stated, however, that in some of these cases the mixed infection was found at autopsy and, as is well known, terminal infection or postmortem invasion with coccus forms is not uncommon, whereas such invasion by influenza bacilli is most unusual. It is, therefore, not improbable that most of these cases were primary influenza infections.

A sufficient number of cases has now been observed to establish the fact that influential meningitis is a disease of infants and young children and is extremely rare in adults. Over one-half the cases reported in the literature occurred in children under one year and the youngest child afflicted was 10 weeks (Fraenkel's first case). The patient whose case is here reported is the youngest on record, being 9 days old at the time of death. The infection was probably acquired four or five days previously.

According to the clinical report there was little evidence of meningeal trouble, enteritis being the chief clinical finding noted. The birth was normal. The postmortem examination confirmed the intestinal involvement and revealed the presence of a mild peritonitis, not recognized macroscopically, and influenza bacilli in pure growth in the peritoneal cavity. The question arises in this case as to the possibility of the intestinal lesions being primary and the involvement of the peritoneum and meninges secondary. Cultures of the intestinal contents unfortunately were not made in this case, and, since little or nothing is known about the occurrence of influenza bacilli in the intestinal canal, definite statements can not at present be made. In the literature the primary foci are variously given, the lungs, bronchi, middle ear and nasal cavities being the sources chiefly suspected. Some of the cases are regarded as generalized infections, since multiple abscesses occurred before or fol-

1. Adams: Arch. Pediat., 1907, xxiv, 721.
2. Cohoe: Am. Jour. Med. Sc., 1909, cxxxvii, 74.

lowing the meningeal involvement (Slawyk, Dudgeon, Adams). In a few no statements are made about the primary focus or, as in the present case, the portals of entry usually suspected are entirely normal. A common symptom in these cases, however, is diarrhea, and in a considerable number a well-marked enteritis has been found at autopsy. The intestinal tract apparently has thus far not been suspected as an atrium by any of the writers, notwithstanding the common occurrence of lesions at this point; and, while such an origin may be uncommon, cases like the one here reported lead one to suspect strongly such a possibility. There are no data at hand which will enable one to decide this question definitely, but in the absence of other lesions, especially of the respiratory tract, nasal cavities, middle ear, etc., the intestinal origin seems very probable.

In few of the cases have extensive bacteriologic studies been made. Slawyk[3] obtained the bacilli from the blood, from abscesses, meningeal exudate and lungs; others have obtained the bacilli from the spleen. In none of the cases have the bacilli been recovered from the peritoneal cavity, and peritonitis is not mentioned as a complication in any instance. Fisch and Hill[4] report a case of purulent peritonitis from the exudate of which the influenza bacillus was isolated in pure culture, but meningeal symptoms did not exist. In the present case it is possible that the presence of the influenza bacilli and the slight exudate in the peritoneum resulted from an influenzal bacteriemia, for it is probable that this occurred, notwithstanding the absence of the bacilli in the heart's blood after death. Certainly the peritoneal involvement is much more recent than the meningitis and it may be simply a terminal affair.

The general appearance of the brain and meningeal exudate answers very well to the description of influenzal meningitis given by other writers. I may refer particularly to the excellent colored plate illustrating Fraenkel's paper on this subject,[5] which bears a close resemblance to the picture in this present case. A striking feature is the greenish-yellow, highly purulent, friable exudate, and, as has been pointed out by Fraenkel, Ghon and others, the small amount, or total absence of, fibrin as shown microscopically by special fibrin stains. In the formalin-fixed tissue of this case the exudate appears to contain very little fibrin and is made up almost entirely of cells, chiefly of the polymorphonuclear variety. In certain places large endothelial cells also are found

3. Slawyk: Ztschr. f. Hyg. u. Infectionkr., 1899, xxxii, 443.
4. Fisch and Hill: St. Louis Med. Review, 1903, xlviii, 19 and 55.
5. Fraenkel: Ztschr. f. Hyg. u. Infectionkr., 1898, xxvii, 315.

ingesting other cells. A feature distinguishing this form from other forms is the very large number of bacilli in the exudate, both inside and outside the polymorphonuclear cells. In meningococcus meningitis the organisms are never so numerous. In pneumococcus and streptococcus infections the organisms may occasionally be as numerous, but phagocytosis is either very slight or entirely absent.

Changes in the underlying brain substance are limited to a very slight infiltration of leucocytes and plasma cells immediately beneath the pia, while deeper in the tissue and along the blood vessels little or no change occurs. This agrees with the findings of others in such cases.

Ghon and Fraenkel state that it is not possible to distinguish influenzal meningitis from that produced by the meningococcus or pneumococcus, except by bacteriologic means. This is undoubtedly true in many cases. The descriptions of influenzal meningitis given in the literature, however, indicate that the exudate as a rule is highly purulent and more copious and wide-spread than that commonly observed in other forms. Cellular differentiation of the exudate will not aid, and clinically there is surely no reliable means. It may be stated that a highly purulent, massive, meningeal exudate, occurring in an infant or young child, is suggestive of this form, and the influenza bacilli should be sought for by proper methods on hemoglobin media. In fact, blood media should be used as a routine in the examination of all meningeal and spinal fluids.

A study of the morphological and biological properties of the influenza bacilli isolated in this case reveals no essential differences from those of the bacilli so commonly found in the sputa in various infectious diseases. The property of symbiosis is well marked; the small colonies present the typical dewdrop appearance, and are not hemolytic and grow only on hemoglobin media, with a preference for pigeon blood agar. The bacilli show only a slight tendency to form threads; are Gram-negative and distinctly bipolar when stained; very susceptible to phagocytosis; and show some pathogenic power for guinea-pigs. They agree in every detail with a bacillus received from Dr. Wilkinson of Washington, D. C., and recovered from the spinal fluid of a non-fatal case of meningitis occurring in a child during convalescence from whooping-cough.

The occurrence of a similar condition in the twin brother beginning on the same day, running an almost identical course clinically, and terminating fatally three days after the death of the other child, is worthy of note. Unfortunately an autopsy was not made in this case, but the facts strongly suggest a similar infection of common origin in the two cases. As already stated, the mother had previously been well and no

members of the family were afflicted with "colds" or other diseases. Hence the source of the infection in these cases remains obscure.[6].

SUMMARY

Twin brothers became ill on the fifth day after birth; the cases ran an identical clinical course and terminated fatally on the ninth and eleventh days respectively after birth.

There was little or no distinct clinical evidence of meningeal involvement.

Autopsy on the first child revealed as the prominent lesions acute purulent leptomeningitis and acute enteritis.

From the meningeal exudate and from the peritoneal fluid pure cultures of *B. influenzæ* were obtained.

The usual atria of infection—nasal cavity, tympanic cavities, lungs, bronchi and throat—were normal. Omphalitis was not present. The intestinal tract is a suspicious portal of entry.

839 Lakeside Place.

6. Since this article was written Cohen (Ann. de l'Inst. Past., 1909, xxiii, 273) has reported three cases of meningitis in infants caused by an organism belonging to the influenza group. Morphologically and culturally it is identical with Pfeiffer's bacillus but by conglutination tests and reactivation experiments specific differences appear. Cohen believes that this organism is the same as that isolated by others from cases of meningitis and called *B. influenzæ* and that the confusion has arisen because the two organisms can be differentiated only by specific serum reactions. He calls the infection septicemic cerebrospinal meningitis because a septicemia occurs in the human subject and in inoculated animals.

THE CLINICAL SIGNIFICANCE OF THE URINARY NITROGEN

III. NITROGENOUS METABOLISM IN TYPHOID FEVER *

JAMES EWING AND C. G. L. WOLF
NEW YORK

The nitrogenous metabolism of typhoid fever has rarely been the subject of systematic study. It has long been known that this disease, rather more than other continued fevers, is marked by a very high urinary nitrogen excretion, but the partition of this nitrogen and the bearing of variations in the forms of nitrogenous compounds excreted in the urine on the pathology of the disease has received very scant attention. The reason for this paucity of effort lies, not in any supposed lack of importance in the subject, but in the fact that until recently there have been no satisfactory methods for the estimation of the different forms of urinary nitrogen, and no normal standards of comparison. Since both of these deficiencies have recently been met and partly removed there would seem to be opportunity for obtaining more significant results than have yet been secured in this field.

The total nitrogen excretion in urine and feces in typhoid fever has recently been studied in detail by Benedict and Suranyi.[1] The fecal excretion they found comparatively small, forming about 10 per cent. of the total nitrogen eliminated. During the active febrile period and sometimes continuing into convalescence there is a pronounced loss of nitrogen, excretion exceeding ingestion by as much as 10 grams daily, the loss diminishing as the fever subsides. Since they were able to limit this loss to some extent by supplying nitrogen-free diet, they argue at length that the excessive nitrogen elimination of typhoid fever is not evidence of toxic destruction of cell proteins but a result of simple hyperactivity of metabolic functions. They do not discuss the character of the nitrogen partition of the disease, although this consideration would seem to have an important place in the above argument.

Von Jaksch and his assistant Erben[2] have furnished the only systematic, but at the same time very meager, data on the partition of the urinary nitrogen in typhoid fever. Von Jaksch's first reports[3] he had

* This article is the third of a series relating to the same general subject. References to the former articles are: 1. The clinical significance of the urinary nitrogen, Am. Jour. Med. Sc., 1906, cxxxi, 751. 2. The metabolism in the toxemia of pregnancy, Am. Jour. Obst., 1907, lv, 289.

1. Benedict and Suranyi: Ztschr. klin. Med., 1903, xlviii, 290.
2. Erban: Ztschr. f. Heilk., Med. Abt., 1904, new series, v, 33.
3. Von Jaksch: Ztschr. f. klin. Med., 1902, xlvii, 1.

to recall on account of deficiencies in the methods employed. In his second paper[4] he records single complete observations on four febrile cases, each of which showed some increase of amido-acid nitrogen.

Erben in 1905 followed one mild case with seventeen examinations over a period of thirty days. The highest daily excretion of this patient was 19.6 grams. The urea at the height of the fever fell to 74 per cent. of the total nitrogen, but soon rose to 80 per cent. plus. The courses of both the ammonia and the rest nitrogen described curves with two apices, one at the height of the fever, the other three or four days after defervescence. This first elevation Erben ascribed rather indefinitely to the febrile process, and the second rise in the rest nitrogen he ventured to refer to resolution of the enlarged lymph nodes. It is difficult to find grounds for this latter assumption, or a warrant for such deductions from the observation of a single case.

The present study was undertaken in 1905 as a control for the interpretation of results obtained by us in the investigation of the urinary nitrogen in the toxemia of pregnancy. It was also suggested by an impression which one of us has gathered from many sources that typhoid fever, especially in the later stages of severe and fatal cases, is largely an autointoxication. It was thought that the study of the nitrogenous metabolism might indicate to some degree the validity of this conception.

That the character of the nitrogen partition might throw light on the nature of some clinical peculiarities of the disease, might control and supplement the present methods of estimating the condition of the patient and determining the diet, might influence the prognosis, or suggest a basis of relapses in the disease, seemed to fall among legitimate expectations. The prolonged toxemia of typhoid fever commended itself as a favorable field for observations on some of the less known nitrogenous substances of the urine, such as kreatinin, kreatin, and the rest nitrogen. Although the results presented are incomplete, especially in respect to fatal cases of the disease, they are not without interest and may have value in several of the relations mentioned.

The study was pursued also in the hope of establishing some correlation between changes in the urinary nitrogen and histological alterations in the liver.

The fragmentary analyses in Cases 1-11 were made in a preliminary way in 1905, when a few observations in severe and fatal cases were secured through the cooperation of Dr. L. A. Conner. For the more complete observations in Cases 12, 13, and 14 we are indebted to our colleague, Dr. Philip Shaffer, who carried out the analyses in the summer of 1906. In 1907 we were able to observe several cases in Bellevue

4. Von Jaksch: Ztschr. f. klin. Med., 1903, L. 167.

Hospital through the courtesy of Dr. Alexander Lambert. Our expectations of securing complete observations in severe cases during the summer of 1908 were partly disappointed, as the disease in New York during that period proved unusually mild and comparatively rare. Yet three severe cases were observed in New York Hospital through the active interest of Dr. L. A. Conner.

We found it extremely difficult to obtain satisfactory collections of the twenty-four hour urine from stuporous and incontinent typhoid patients, which were the conditions which it was most desired to observe. In females especially these difficulties proved almost insurmountable, so that we would not again attempt such a study in women very sick with typhoid fever. The technical methods employed in this work were those described in our first contribution on the subject of the "Clinical Significance of the Urinary Nitrogen,"[5] and since the general significance of the urinary nitrogenous substances and their normal variations were discussed at some length in that article these topics will not be further considered at this time. It is, however, necessary to point out that a comparison of normal standards in healthy subjects with the metabolism of febrile conditions must be undertaken with caution. For example, we question whether the observations on the influence of starvation in healthy subjects can safely be transferred to febrile conditions.

ANALYSES OF RESULTS

In the analysis of the results the chief interest concerns the relation of the urinary nitrogen and its partition to the clinical symptoms.

TOTAL NITROGEN

The records show a total urinary nitrogen excretion reaching 33.65 gm. in an adult weighing 155 pounds, and 29.07 gm. in another patient weighing 148 pounds, but averaging considerably below 20 gm. during febrile periods in all the cases. With the restricted diet of these patients this large excretion of nitrogen must signify consumption of tissue protein and marked loss of nitrogen on balance. As the diet was uniformly low in nitrogen, consisting of 4 to 6 ounces milk every three hours, or of similar amounts of meat broth, this factor probably does not distinctly influence the total nitrogen. Some considerable variations may be attributable to the activity of the kidneys. There was a general relation between the weight of the patient and the total nitrogen excreted. Estimated according to the weight of the patient the more severe the typhoidal process, as judged by the temperature and general condition,

5. Ewing and Wolf: Am. Jour. Med. Sc., 1906, cxxxi, 751.

the higher the nitrogen output. To this rule, which applies chiefly to the early stages of the disease, there were two important exceptions. In two cases (19 and 20) toward the end of very severe attacks of the disease the total nitrogen was unusually low or even below normal, 3 to 6 gm., while the febrile process continued. In these cases one has to deal with very unusual conditions, such as persistent vomiting, starvation, anemia, and a very low state of vitality. In such states one may reasonably assume that the energy exchange is very low, and that after the system has been extensively depleted the febrile typhoid process may continue without the extensive loss of nitrogen which marks its earlier stages. In several cases (13, 15, 16, and 18) a postfebrile increase in total nitrogen was observed extending over a period of seven days. In two of these cases this increase was coincident with the addition of two and four eggs to the diet; in a third case the amount of meat broth was considerably increased at this time, while in the fourth case (18) no change in the diet was noted. In a fifth case presenting adequate data (17) no postfebrile increase occurred. We are therefore disposed to refer this increase, when it occurs, to changes in the diet and not, as Erben has suggested, to resorption of lymph nodes or any other essential process in the disease. The postfebrile increase in rest nitrogen Erben also refers to the absorption of lymph nodes, but in several of our cases such an increase was clearly explained by the addition of meat to the diet.

Whether an antemortem increase in nitrogen excretion occurs in this disease our observations on fatal cases do not demonstrate, but in Case 9 there is some indication of such a phenomenon. The highest excretion of nitrogen in proportion to the body weight seems to occur in the so-called toxic cases and periods of the disease when the patient appears poisoned and can be observed to be losing weight rapidly. Although these features are usually coincident with a high temperature, the total nitrogen seems to be less affected by the fever than by the intoxication. Thus Patients 18 and 14, weighing 135 and 148 pounds and selected because of the "toxic" character of the disease, excreted 33.65 gm. and 29.07 gm. nitrogen, which is relatively much more than the excretion in the milder cases (15, 17 and 16), 14.3, 16.7 and 8.16 gm. In these cases the patients weighed 123, 117 and 67 pounds respectively, and on the day of these observations had the same temperature, 103° F.

UREA

In the majority of well-marked cases of typhoid fever the urea nitrogen forms a notably high proportion of the total, even when the patient appears to be very sick. In severe stages it usually runs below 80 per

cent. when 12 to 20 gm. of nitrogen are being excreted, while in some cases of recovery it was found below 70 per cent., and even as low as 60 per cent. A ratio below 70 per cent. during febrile stages usually indicated a grave condition. The highest ratio, 88.1 per cent., was observed on the twenty-first day of a severe case (14), in which there was a rapid recovery. A review of our results seems to show that a persistently high urea ratio is a favorable sign, yet two fatal cases on first examination gave over 80 per cent. urea nitrogen. Sharp increases in this ratio are very favorable signs (Cases 2 and 19), while in two cases (8 and 9) sharp decreases, 82 to 67 per cent. and 80 to 60 per cent., in four days, were shortly followed by the death of the patient. In some cases (14, 19, and 22) the urea ratio seemed to be a better index of the patient's condition than were the temperature, pulse, or signs of intoxication.

In several cases with rapid convalescence the urea was constantly above 80 per cent., while in two cases with relapses (15 and 17) and in three (16, 19, and 20), with slow convalescence, the urea ratio tended to remain below 80 per cent.

Our experience leads us, therefore, to place considerable value on the ratio of urea nitrogen in following the course of typhoid fever, since this ratio very often serves as control on other clinical indications, and may be relied on to a considerable extent to reveal the general type of the disease. The observations on the urea ratio in typhoid fever also seem to lend some support to the view that lesions of the liver established in the course of diseases attended with disturbances of nitrogenous metabolism may have considerable influence on the character of this metabolism. Although we were disappointed in not securing extended observations on fatal cases and no autopsies were obtained we are disposed to assume that the severe degeneration and focal necroses which are nearly constant in the liver of fatal typhoid fever were connected with the sudden decline in the urea-forming function in Cases 8 and 9.

During a febrile convalescence somewhat different interpretations of changes in the urea nitrogen ratio seem to be required from those applying to the febrile period. Starvation acidosis or abrupt addition of meat to the diet appeared to be responsible for low urea ratios in Cases 19 and 20.

AMMONIA NITROGEN

In one fatal case (9) the ammonia ratio reached 8.9 per cent. (2.09 gm.). In one case (15), preceding a relapse, it failed to reach the low level commonly observed. In two very severe cases (19 and 20) during convalescence ammonia nitrogen ratios of 10 per cent. and 14.5 per cent.

seemed referable to slight starvation acidosis. At all other times the ammonia ratio was not distinctly above normal, and often it was uniformly low. The present observations, therefore, do not indicate that acidosis is a prominent feature of typhoid fever. Even the highest figures observed indicate only moderate grades of acidosis, especially for patients on a restricted milk diet. With a sharp onset of typhoid fever one would expect to find considerable acidosis and excess of ammonia from deficiency of food, but none of our cases was observed at the onset of the disease. Since acidosis arises from the incomplete burning of fats in the absence of carbohydrates, the relative lack of acidosis in typhoid fever may arise from a pronounced tendency toward the consumption of proteins rather than fats. There are many indications, however, that during fever the complete combustion of fats may be effected without the presence of recently ingested carbohydrates. Or the carbohydrate radicles of the proteins may be sufficiently available for the complete combustion of fats. In any case, patients suffering from typhoid fever and on practically a starvation diet are comparatively free from acidosis. Many have insisted that the total ammonia excretion rather than its ratio to the total urinary nitrogen should be taken as the index of acidosis. In many conditions in which the total nitrogen is not high this rule is clearly applicable. Yet ammonia possibly has other functions besides that of neutralizing acids, and with every increase in total nitrogen there is normally an increase in absolute ammonia nitrogen. In typhoid fever with a daily excretion of 15 to 25 gm. nitrogen one can attribute no pathological significance to a moderate excess over the total ammonia excretion of health which has been established by Folin at about 6.7 gm. In typhoid fever the total ammonia does not usually much exceed this figure. Increased acetone has been found by von Jaksch, and beta-oxybutyric acid by von Noorden. The acetone bodies were not estimated in the present cases.

KREATININ

The observations on the excretion of kreatinin and kreatin in typhoid fever seem to have important bearing not only on the metabolism of this disease but on the general physiological significance of these substances. It has been pointed out by Folin[6] that the chief factor determining the elimination of kreatinin is the weight of the person, and he has further defined this factor as the mass of active protoplasmic tissues. Shaffer[7] has shown that the hourly excretion of kreatinin is remarkably uniform.

6. Folin, O.: Am. Jour. Physiol., 1905, viii, 85.
7. Shaffer, P.: Proc. Am. Soc. Biol. Chem., 1907, i, 22. Am. Jour. Physiol., 1908, xxii, 445. Am. Jour. Physiol., 1908, xxiii, 1.

that it is unaffected by great changes in the amount of protein ingested, by diuresis, or by active exercise. There is, therefore, a somewhat fixed relation between the kreatinin excreted and the body weight of the subject, which Shaffer expresses as the "kreatinin coefficient," indicating the milligrams of kreatinin nitrogen per kilo of body weight. This coefficient he finds to vary in healthy subjects between 11.7 and 5.4, average 8.4. Very similar coefficients, 8.2 to 7, have been established for dogs by Wolf and Osterberg.[8]

Folin suggested that kreatinin excretion is an index of total endogenous or tissue katabolism, but from studies in various pathological conditions, especially in Graves' disease, Shaffer would limit the sources of urinary kreatinin chiefly to the muscles and would interpret the kreatinin coefficient as the expression of muscular and perhaps general cellular efficiency. Similar conclusions were reached by Spriggs,[9] who found low coefficients in cases of muscular dystrophy, amyotonia congenita, and myasthenia gravis. This view is also strongly supported by the observations of Amberg and Morrill,[10] who found very low kreatinin coefficients in new-born infants whose muscles are imperfectly developed. A relatively high excretion observed in some fevers Shaffer ascribes to pathological increase in the kreatinin-forming process, coincident with the destruction of body proteins and due to high temperature or the action of bacterial toxins.

On the other hand, Mellanby,[11] from an extensive study of the formation and excretion of kreatinin and kreatin, introduces an entirely new point of view in concluding that kreatinin is formed in the liver and is in part converted into kreatin and thus stored in the muscles until the amount of kreatin in the muscles reaches the saturation point, after which the excess of kreatinin continually formed in the liver is excreted in the urine. In cases of hepatic cirrhosis and cancer he found low kreatinin excretion, and in general he is inclined to regard kreatinin excretion as an index of hepatic efficiency.

In the present cases the records show that kreatinin excretion is increased during the active periods of typhoid fever and diminishes during convalescence. The total quantity bears a distinct relation to the patient's weight and muscular development. The highest amount observed, 1.06 gm. (K. C. 15.9), was on the twenty-first day of a severe febrile case (14) in a muscular subject, and the lowest amount seen in

8. Wolf and Osterberg: Biochem. Ztschr., 1907, v, 304.
9. Spriggs: Quart. Jour. Med., 1907, i, 63.
10. Amberg and Morrill: Jour. Biol. Chem., 1907, iii, 311.
11. Mellanby: Jour. Physiol., 1908, xxxvi, 447.

an uncomplicated case, 0.16 gm. (K. C., 5.7), occurred in a young boy (16) during convalescence. In general it may be said that in adults suffering from typhoid fever a kreatinin excretion of over 0.5 gm. belongs to the febrile period, while during convalescence the kreatinin nitrogen usually falls below 0.5 gm. In one case (20), that of a young girl greatly emaciated and very anemic, it fell to 0.13 gm. (K. C., 3.6) on the forty-third day in convalescence.

There is thus distinct evidence of a pathological increase in kreatinin excretion belonging to the typhoid process. The highest quantities and the highest coefficients appear in the severe stages of the disease, while the absolute amounts diminish with convalescence and some very low coefficients appear in emaciated and very weak subjects (Cases 19 and 20).

These results do not enable one to decide between the merits of the contending hypotheses regarding the significance of kreatinin.

During fever all the processes normally involved in nitrogenous metabolism seem to proceed in increased volume, so that the liver, while concerned in elaborating enormous amounts of urea, may also, according to Spriggs, be preparing an excess of kreatinin which overflows from the muscles to the urine; or, according to Shaffer, the increased muscle metabolism directly yields an excess of kreatinin. The peculiar muscular weakness which marks the onset and course of typhoid fever very probably resides chiefly in disturbed innervation, and the high kreatinin excretion at such periods may properly be interpreted as of toxic significance. The very low kreatinin coefficients observed in some very weak and emaciated subjects (as Cases 19 and 20), and the much higher coefficients found in other patients who withstood the disease more successfully, favor Shaffer's hypothesis. The present data do not seem to offer any new basis for the discussion of the relation of kreatinin to kreatin.

KREATIN

Kreatin appeared in the urine nearly constantly in the active periods of the disease and disappeared during convalescence. Its appearance is coincident with the period of negative nitrogen balance and general loss of weight. The highest amount observed was 1 gm. kreatin nitrogen on the sixth day of a severe case (18), when the total nitrogen reached the highest figure in our series, 33.65 gm., with a nitrogen loss on balance of 30 gm., while the temperature rose to 103 F. The patient then weighed 155 pounds and was losing flesh in the rapid manner characteristic of severe typhoid fever. At this time the kreatin nitrogen was

nearly three times as abundant as the kreatinin nitrogen. Also in Case 20 the kreatin nitrogen several times exceeded the kreatinin nitrogen.

The kreatin was rather sensitive to slight disturbances of temperature during convalescence, persisting throughout the slow recovery of Patients 16 and 20 and reappearing with a slight rise of temperature in Case 14. Yet it disappeared before full defervescence in Case 17 and failed to reappear in a mild relapse in Case 15. As a rule the kreatin nitrogen was low in the milder cases and its disappearance from the urine proved a favorable sign.

These features are consistent with the view expressed by Shaffer, that kreatin is a product of the destruction of muscle protein.

URIC ACID

The uric acid nitrogen varied considerably from day to day, but always within limits that may be regarded as normal. It was highest (maximum 0.46 gm.) in the febrile periods and in general exhibited a declining tendency with the fever but failed to show any definite relation to the clinical features. A very low excretion may be noted in one case (15) over a period of four days, during which the temperature was 103° F., while in Case 17 there was some indefinite indication of the posteritical increase reported by Gordes.

REST NITROGEN

Changes in the rest nitrogen presented some of the most significant features of the metabolism. Since a fall in urea nitrogen is usually coincident with a rise in rest nitrogen, most of these features have already been indicated in the discussion on urea. During severe febrile periods of favorable cases the urea runs high and the rest nitrogen low, but in graver conditions the urea tends to fall below 70 per cent. and the rest nitrogen rises toward or above 20 per cent. In two fatal cases (8 and 9) extensive rises in the rest nitrogen to 23.76 per cent. and 26.57 per cent. (6.24 gm.), with corresponding falls in urea, occurred shortly before death. In these fatal cases the urinary sediment contained crystals resembling leucin. We believe, therefore, that the high rest nitrogen of such cases signifies in some degree defective urea forming function of the liver.

Since the diet during the severe febrile stages of the disease was very low and uniform an influence on the rest nitrogen from this source may be excluded. During convalescence, however, striking variations in the rest nitrogen seemed clearly referable in several cases, notably in 19 and 20, to the addition of meat to the diet. We interpret this result

as indicating that the organism was at that time unable to metabolize fully the products of digestion of protein food, which therefore passed out in the urine unchanged. This observation may be brought in accord with the experiments of Glaessner,[12] who found that feeding amino-acids in certain diseases of the liver was followed by their excretion unchanged in the urine.

The significance of high rest nitrogen in the active febrile and in the convalescent afebrile stages of typhoid fever, if our interpretation proves correct, is therefore essentially different. In the former period it represents endogenous metabolism; in the latter it may indicate imperfect exogenous or food metabolism. It is obvious that this observation may throw light on the significance of the rest nitrogen in many other conditions, and especially in those in which the diet varies. For example, a rest nitrogen ratio of 20 per cent., as often observed in moribund cases of acute yellow atrophy in which little or no food has been taken for several days, may have quite a different significance from that of a similar ratio occurring in a case of constipation in an overfed but otherwise healthy subject.

While the greater significance of the changes referable to endogenous metabolism may readily be granted, it should be noted that in some of our patients (10 and 16) the addition of meat to the diet, and a consequent rapid rise in rest nitrogen, was marked by a considerable rise in the pulse and temperature and distinct discomfort to the patient. Such disturbances in typhoid fever are commonly referred to "indigestion." "*Febris carnis*" is a long-recognized feature of the dietetics of typhoid fever and other diseases. It has been variously interpreted, but would seem to receive an adequate explanation in the present urinary analyses.

In several cases (12, 14, 15, 16, and 18) we have noted the combination of increased rest nitrogen, increased indicanuria, soon followed by albuminuria.

In some instances these features followed the addition of meat or eggs to the diet, while, at the same time, some disturbance of the pulse and subjective condition was commonly observed. These attacks, like the former, may probably be interpreted as the result of imperfect metabolism of digested and putrefaction of undigested protein food.

Reviewing the data of the foregoing report, perhaps the most notable feature is the demonstration that the severest symptoms of typhoid fever, including high temperature, stupor, and incontinence, may be tolerated with practically a normal urea formation. In Case 22 only

12. Glaessner: Ztschr. f. exper. Path. u. Therap., 1907, iv, 336.

the high total nitrogen, the kreatinin, and the kreatin would suggest that the patient was not in a normal state of health. This patient's tissues, however, were partly protected by the ingestion of considerable food and he made a rapid and complete recovery. On the other hand, in fatal cases the nitrogenous metabolism is badly deranged, with a sharp fall in urea nitrogen and corresponding rise in rest nitrogen, showing that in these cases the fatal issue was marked by a collapse in the urea forming function of the organism. Between these two extremes fall many cases with varying grades of metabolic disturbance and generally with corresponding departure from the most favorable clinical course.

These observations on the integrity of the urea-forming function in severe typhoid fever may be interpreted as favoring the belief of Benedict and Suranyi that the excessive nitrogen elimination of typhoid fever is not evidence of toxic destruction of cell proteins but a result of simple hyperactivity of metabolic functions. Yet these patients are often extremely ill; they present the clinical signs of intoxication, including stupor, subsultus, and rapid emaciation; and, unless one chooses to call nothing toxic which is not abnormal in type, the very activity of the nitrogenous metabolism in typhoid fever must be included as a factor in the morbid complex of the disease. That this hyperactivity is not directly connected with the neutralization of typhoid endotoxins may readily be granted without lessening its importance as a source of morbid phenomena in the disease. Moreover, the excessive urea formation is associated with high excretion of kreatin and kreatinin, which are distinctly abnormal features of metabolism.

Since in the so-called fatal toxic cases this hyperactivity of the urea-forming function is not maintained, one must conclude that death in these cases is partly referable to a loss of efficiency in these overacting functions. If this conclusion is correct it offers support to the view that fatal uncomplicated typhoid fever is largely an auto-intoxication, in all the essential particulars in which that condition is now understood.

A second fact of special interest in these data is the different significance which seems to belong to the rest nitrogen in severe febrile stages of the disease in patients taking little or no protein food, from that attaching to the rest nitrogen in convalescent cases when protein food is first added to the diet. In the former condition a high rest nitrogen would seem to indicate that the endogenous metabolism is faulty and that the organism fails to synthesize urea even from its own native ingredients. Under these conditions a high rest nitrogen indicates a grave defect in metabolic functions. In convalescence, however, when the endogenous metabolism is practically normal, the organism is un-

able properly to metabolize ingested alien amino-acids which pass out in the urine unchanged. Here the resulting high rest nitrogen is of much less serious significance, although sometimes attended with subjective disturbances.

These observations on the occurrence of high rest nitrogen in two periods of typhoid fever seem to us to support the view that the anatomical alterations in the liver of typhoid fever are essentially connected with the disturbance of metabolism. They also suggest caution in the early addition of meat to the diet of convalescent typhoid patients.

In several cases, notably on the thirty-eighth day in Case 16, the simultaneous occurrence of increased rest nitrogen, indicanuria, and albuminuria was noted and often subjective symptoms were added, such as fever, acceleration of pulse, vomiting, and general discomfort. The increased rest nitrogen in these cases we interpret as the result of defective function of the liver and failure to change amino-acids into urea. . An excessive formation of indol, from intestinal putrefaction, may be a factor in the disturbance by interfering with the nutrition of this organ. These observations, which we have duplicated in the toxemia of pregnancy seem to explain the *febris carnis,* and may be of significance in the etiology of nephritis and in the relation of disturbances of the liver to Bright's disease. Whether attacks of this character have any relation to relapses in the disease has not been demonstrated in these data, but it would seem not improbable that disturbances in metabolism may have important influence in this direction.

Finally, the most obvious conclusion of this study is the inadequacy of the diet used in these cases and of that generally employed in typhoid fever. When a patient is losing 20 to 30 gm. of nitrogen daily on balance it can not be said that any success is being attained in combating the most important feature of the metabolic disturbance in the disease.

REPORTS OF CASES

CASE 14.—*Patient.*—Muscular negro, aged 26, normal weight, about 165 or 170 pounds, admitted to Bellevue Hospital March 19, 1907, service of Dr. Alexander Lambert. He had lost considerable flesh before admission and on the twenty-second day weighed 148 pounds; on the thirty-second day, 139 pounds; on the thirty-eighth day, 148 pounds. Blood examination on the seventeenth day gave 5,600 leucocytes, 50 per cent. polynuclear; Widal reaction positive and culture positive. The patient presented the appearance of a rather toxic type of the disease. He emaciated rapidly and the mental condition was somewhat stuporous, although the temperature was not high. These features coincide with the high nitrogen output. The nitrogen partition, however, was normal, the urea ratio being one of the highest observed in this series of cases, and this fact we are disposed to connect with the rapid and complete recovery and the freedom from com-

plications. The case suggests a dependence of the toxic condition on the excessive protein destruction, and raises the question whether these toxic features might not have been reduced if the protein destruction could have been prevented.

Diet.—On the ninth and tenth days the patient received 2.8 gm. N, 75 calories, in the form of chicken broth and gelatin, and excreted 23.5 and 28.7 gm. N, a total loss of 46.6 gm. in the two days. On the following five days he received 2.9 gm. N, 171 calories, and excreted 29 to 21 gm. N. On the twenty-eighth day the diet was raised to 311 calories with 3.9 gm. N. Thereafter there was a steady fall in nitrogen excretion, except on the thirty-third day, when 27.2 gm. were

TABLE 1.—URINARY ANALYSES, CASES 1 TO 11 *

Case No.	Day of Disease.	Volume c.c.	Total Nitrogen Grm.	Urea N %	Ammonia N %	Rest N %	Albumin.	Temp.	General Condition.
1.	21	1100	16.72	64.2	2.9	15.21	++	104.2	
	22	740	11.94	77.	2.8	13.1	++	101.	Brighter.
2.	26	865	15.78	73.4	4.34	18.82	O	102.5	Restless.
	30	1210	17.67	85.5	1.89	9.43	O	103.5	Comfortable.
3.	26	1135	7.12	78.9	4.1	11.6	O	99.	Comfortable.
	28	1200	6.6	78.7	7.7	8.9	+	99.2	
4.	7	460	.....	78.0	5.63	15.7	++	108.5	Acute nephritis.
5.	24	325	.....	75.7	2.21	20.6	+	102.5	Died 25th day.
6.	16	365	.....	66.4	6.68	22.9	+	102.	Serious.
7.	14	960	12.20	69.5	1.96	9.85	+	104.	Delirious.
	16	1100	13.33	66.8	2.17	11.3	+	104.	Delirious.
8.	33	760	7.80	81.9	3.4	9.69	+	100.	Delirious. Incontinent.
	37	330	.....	67.0	6.12	23.76	+	100.5	Died 41st day.
9.	26	760	18.4	80.13	7.91	7.82	+	105.	Incontinent. Dull.
	30	1330	23.5	60.27	8.9	26.57	+	105.	Stupor. Died 32d day.
10.	35	990	19.2	74.9	5.81	13.4	+	104.	Fair.
	41	500	10.2	72.5	6.47	13.5	+	103.5	Fair.
11.	10	1400	15.7	77.2	5.29	14.12	+	104.5	Fair.
	25	460	.....	80.3	3.45	14.9	+	105.5	Relapse.

* In these cases the rest N was determined directly by the Pfaundler method.

eliminated. The heat value and nitrogen content of the food were also raised on the thirty-third day to 5.5 gm. N and 798 calories; on the thirty-fifth day to 6.8 gm. N and 1,360 calories; on the thirty-seventh day to 9.0 gm. N and 1,845 calories.

CASE 15.—*Patient.*—Man, aged 26, admitted to Bellevue Hospital, March 24, 1907, service of Dr. Alexander Lambert; weight, eighteenth day, 123 pounds; thirty-second day, 109 pounds; thirty-seventh day, 115 pounds; forty-third day, 119 pounds. On the twentieth to twenty-third days the patient was dull by day, restless at night, and complained of abdominal pain, diarrhea, epistaxis, anorexia; from the twenty-fourth day comfortable. Blood examination gave 9,500 leucocytes,

60 per cent. polynuclear. Widal incomplete, culture positive. The relapse about the forty-fourth day was associated with pharyngitis and indicanuria, but without typhoidal symptoms.

TABLE 2.—URINARY ANALYSES, CASE 12

Day of Disease.	Volume.	Total Nitrogen.	Urea N.		NH_3 N.		Kreatinin N.		Uric Acid. N.		Rest N.		Albumin.	Temp.	General Condition.
		Gm.	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%		99	
24	760	10.03	8.01	79.8	0.90	8.9	0.193	1.9	.15	1.4	.78	8.0	O	102.5	Comfortable.
														100	
25	1300	18.67	14.9	80.2	1.00	5.4	.47	2.5	.29	1.6	1.9	10.3	O	102	Comfortable.
														101.5	
26	1135	18.20	14.2	77.9	1.16	6.4	.43	2.3	.27	1.5	2.2	11.9	O	98.6	Comfortable.
														100.2	
27	1470	16.40	13.5	82.8	1.04	6.4	.37	2.3	.26	1.6	1.2	7.2	O	99	Comfortable.
														100.2	
29	1510	26.80	20.2	75.3	1.66	6.2	.64	2.4	.42	1.6	3.9	14.5	O	98.6	Comfortable.
														99	
32	670	9.35	7.56	80.9	0.46	4.9	.24	2.6	.16	1.7	.93	9.9	+	98.6	Comfortable.
														99	
34	970	10.30	8.20	79.4	0.59	5.7	.25	2.4	.13	1.2	1.14	11.0	+	101	Headache.
														101	
35	.....	.....	.....	....	....	...	...	...	...	...	....	....		104	Relapse.

TABLE 3.—URINARY ANALYSES, CASE 13

Day of Disease.	Volume.	Total Nitrogen.	Urea N		NH_3 N.		Kreatinin N.		Uric Acid. N.		Rest N.		Albumin.	Temp.	General Condition.
		Gm.	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%		102	
13	1475	27.40	23.3	85.0	1.61	5.9			.32	1.2	.22	7.9	O	99.5	Fairly Good
														100	
14	665	12.47	10.1	81.1	0.70	5.6	.36	2.9	.19	1.5	1.1	8.9	O	99.2	Good.
														99.6	
15	325?	5.95	4.88	8.27	0.29	4.8	.16	2.7	.08	1.3	0.5	8.5	O	98.6	Good.
														99.8	
17	985	10.90	9.14	84.0	0.55	5.0	.30	2.9	.17	1.6	0.7	6.5	O	98.6	Good.
														99.6	
18	1080	12.25	10.5	87.0	0.51	4.1	.33	2.7	.18	1.5	.58	4.7	O	98.6	Good.
														99	
21	2075	16.45	14.7	85.7	0.74	4.5	.42	2.5	.15	0.9	1.38	8.4	O	98.6	Good.
														99.4	
23	2225	19.20	16.6	86.6	0.85	4.4	.49	2.5	.19	1.0	1.1	5.5	O	98.6	Good.
														99.8	
28	1900	20.95	18.5	88.2	0.95	4.5	.47	2.2	.19	.09	0.9	4.2	O	98.4	Good.

This case represents a sharp attack of typhoid fever rapidly improving. The chief point of interest is the rapid change in the nitrogen partition coincident with improvement in the clinical status. The considerable loss of weight and the rather low urea N seem to coincide as features of a somewhat severe typhoidal process.

Diet.—From the fourth to eighth days the patient received chicken broth, jelly and crackers; total N content, 3.60 gm. During this time the N elimination varied between 13 and 14 gm., a loss per day of about 10.0 gm. On the sixteenth day eggs and rice were given, increasing the nitrogen ingested to 5.51 gm. and

TABLE 4.—URINARY ANALYSES, CASE 14

Day of Disease	Volume c.c.	Sp. Gr.	React.	Albumin.	Indican.	T—N	Gross Urea N.		NH_3 N.		Urea N.		Kreatinin N.		Kreatin N.		Uric Acid N.		Rest N.		Kreatinin Coefficient	Temp.
						Gm.	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%		
21	1330	1021	acid	+	+	23.54	21.52	91.4	0.78	3.3	20.74	88.1	0.76	3.2	0.11	0.4	0.23	1.0	0.92	4.0	11.3	102.4
22	1740	1022	acid	+	+	28.7	25.40	88.5	1.01	3.5	24.39	85.0	1.06	3.7	0.00	0.0	0.23	0.8	2.01	7.0	15.9	102.8
23	1700	1021	acid	+	O	29.07	24.14	83.0	0.82	2.8	23.32	80.2	0.83	2.8	0.26	0.9	0.32	1.1	3.52	12.2	12.5	103
24	1300	1022	acid	+	O	22.50	19.02	84.5	0.78	3.5	18.24	81.0	0.46	2.0	0.53	2.4	0.30	1.3	2.19	9.8	6.9	102
25	1600	1021	acid	+	O	28.65	24.50	85.5	0.88	3.1	23.62	82.4	0.98	3.4	0.30	1.0	0.37	1.3	2.50	8.8	14.7	101
26	1300	1021	acid	+	O	21.05	18.20	86.4	0.68	3.2	17.52	83.2	0.68	3.2	0.51	2.4	0.27	1.3	1.39	6.7	10.2	100.5
27	1340	1020	acid	O	+	20.90	17.89	85.6	0.25	1.2	17.64	84.4	0.80	3.8	0.59	2.8	0.10	0.5	1.52	7.3	12.0	100
28	1540	1020	acid	+	O	23.10	19.83	85.9	0.65	2.8	19.18	83.1	0.95	4.1	0.51	2.2	0.22	0.9	1.59	6.9	14.3	100.2
29	1090	1023	acid	+	O	18.25	15.51	85.0	0.23	1.3	15.28	83.7	0.81	4.4	0.20	1.1	0.19	1.0	1.54	8.5	12.2	99.2
30	1570	1017	acid	+	O	18.50	15.95	86.2	0.63	3.4	15.32	82.8	0.82	4.4	0.11	0.6	0.22	1.2	1.40	7.6	12.3	98
31	1390	1016	acid	+	O	16.80	14.23	84.7	0.57	3.4	13.66	81.3	0.76	4.5	0.18	1.1	0.22	1.3	1.41	8.4	11.4	99
32	1600	1014	acid	O	+	15.04	12.86	85.5	0.59	3.9	12.27	81.6	0.74	4.9	0.08	0.5	0.21	1.4	1.15	7.7	11.8	99
33	1400	1016	acid	O	++	27.27	25.94	93.5	0.42	1.5	25.52	92.0	0.67	2.4	0.04	0.2	0.15	0.5	0.97	3.4	10.6	98
34	3780	1006	acid	O	O	13.61	11.34	83.6	0.76	5.6	10.58	78.0	0.76	5.6	0.00	0.0	0.23	1.7	1.28	9.1	12.1	99
35	2740	1008	acid	O	O	13.02	10.90	83.7	0.66	5.1	10.24	78.6	0.79	6.1	0.00	0.0	0.22	1.7	1.11	8.5	12.6	99
36	3170	1007	acid	+	+	12.74	10.74	84.3	0.70	5.5	10.04	78.8	0.70	5.5	0.00	0.0	0.32	2.5	[illegible]	7.7	11.1	98.2
37	2490	1007	acid	++	++	11.21	8.74	78.0	0.72	6.4	8.02	71.6	0.37	3.3	0.17	1.5	0.08	0.7	1.85	16.5	5.9	99
38	2860	1007	acid	+	++	12.54	10.90	86.9	0.60	4.8	10.30	82.1	0.37	2.9	0.23	1.8	0.20	1.6	0.84	6.8	5.9	100.5

TABLE 5.—URINARY ANALYSES, CASE 15

Day of Disease.	Volume c.c.	Sp. Gr.	Reaction.	Albumin.	Indican.	Total N. Gm.	Gross Urea N.		NH_3 N.		Urea N.		Kreatinin N.		Kreatin N.		Uric Acid N.		Rest N.		Kreatinin Coefficient.	Temp.
							Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%		
5	730	1023	acid	+	O	14.30	10.56	73.8	0.94	6.6	9.62	67.2	0.42	2.9	0.00	0.0	0.28	2.0	3.04	21.3	6.8	103.5
6	760	1021	acid	+	+	14.61	12.22	83.6	1.32	9.0	10.90	74.6	0.55	3.8	0.28	1.9	0.05	0.4	1.51	10.3	9.0	103
7	660	1020	acid	+	++	13.26	10.90	82.2	1.11	8.4	9.79	73.8	0.48	3.6	0.15	1.1	0.06	0.8	1.67	12.3	7.8	103
8	640	1023	acid	++	+	13.07	10.53	80.6	0.91	7.0	9.62	73.6	0.56	4.3	0.10	0.8	0.01	0.1	1.87	14.2	9.1	103.4
9	810	1022	acid	++	+	15.65	12.70	81.1	1.17	7.5	11.53	73.6	0.60	3.8	0.32	2.0	0.02	0.1	2.01	13.0	9.8	102.2
10	930	1021	acid	+	O	17.26	14.22	82.4	1.18	6.8	13.04	75.6	0.56	3.2	0.28	1.6	0.30	1.7	1.90	11.1	9.1	103
11	1390	1014	acid	+	+	15.03	12.51	83.2	1.49	9.9	11.02	73.3	0.71	4.7	0.07	0.5	0.27	1.8	1.47	9.8	11.6	102.5
12	2060	1009	acid	+	O	12.97	10.73	82.7	1.24	9.6	9.49	73.1	0.62	4.8	0.10	0.8	0.27	2.1	1.25	9.6	10.1	102.6
13	1780	1013	acid	O	+	12.28	9.96	81.1	1.00	8.1	8.96	73.0	0.52	4.2	0.18	1.5	0.28	2.3	1.34	10.9	8.5	102
14	1200	1016	alk.	+	++	10.72	8.17	76.2	0.62	5.8	7.55	70.4	0.36	3.4	0.22	2.1	0.17	1.6	1.80	16.7	5.9	99.4
15	2370	1008	alk.	O	++++	10.73	8.79	81.9	0.92	8.6	7.87	73.3	0.36	3.4	0.31	2.9	0.21	2.0	1.06	9.8	5.9	100.2
16	1770	1011	acid	O	+++	12.41	10.11	81.5	0.62	5.0	9.49	76.5	0.44	3.5	0.30	2.4	0.30	2.4	1.26	10.2	7.2	98.4
17	2870	1007	acid	O	++	11.48	9.76	85.0	0.80	7.0	8.96	78.0	0.46	4.0	0.00	0.0	0.23	2.0	1.03	9.0	7.4	98.2
18	2650	1007	acid	O	+	10.58	8.89	84.0	0.53	5.0	8.36	79.0	0.48	4.5	0.00	0.0	0.24	2.3	0.97	9.2	7.8	99
19	3125	1007	acid	O	++	14.34	11.74	81.9	0.62	4.3	11.12	77.6	0.47	3.3	0.00	0.0	0.25	1.7	1.88	13.1	7.7	98
20	2855	1007	acid	O	+	11.78	10.37	88.0	0.57	4.8	9.80	83.2	0.43	3.6	0.00	0.0	0.20	1.7	0.78	6.7	7.2	98
		Relapse.																				
29	1925	1008	acid	O	++	8.37	7.62	91.1	0.52	6.2	7.10	84.9	0.27	3.2	0.00	0.0	0.08	1.0	0.40	4.7	4.4	101.2
30	3020	1007	acid	O	+++	12.53	11.18	89.2	0.85	6.8	10.33	82.4	0.57	4.5	0.00	0.0	0.27	2.2	0.51	4.1	9.3	100
31	3300	1004	acid	O	+	8.25	7.03	85.2	0.63	7.6	6.40	77.6	0.40	4.8	0.00	0.0	0.17	2.1	0.65	7.9	6.5	99
32	3320	1004	alk.	O	+	8.36	7.50	89.7	0.73	8.7	6.77	81.0	0.46	5.5	0.00	0.0	0.20	2.4	0.20	2.4	7.5	99
33	4490	1003	alk.	O	+	9.02	8.08	89.6	2.07	23.0?	6.01	66.6	0.49	5.4	0.00	0.0	0.22	2.4	0.23	2.6	8.0	98

TABLE 6.—Urinary Analyses, Case 16

Day of Disease.	Volume c.c.	Sp. Gr.	Reaction.	Albumin.	Indican.	Total N. Gm.	Gross Urea N. Gm.	Gross Urea N. %	NH_3 N. Gm.	NH_3 N. %	Urea N. Gm.	Urea N. %	Kreatinin N. Gm.	Kreatinin N. %	Kreatin N. Gm.	Kreatin N. %	Uric Acid N. Gm.	Uric Acid N. %	Rest N. Gm.	Rest N. %	Weight, Kilos.	Kreatinin Coefficient.	Temp.
17	850	1015	acid	O	+	8.16	6.65	81.5	0.33	4.0	6.32	77.5	0.30	3.7	0.11	1.3	0.21	2.6	0.89	10.9	30.6	9.8	103.2
18	1040	1015	acid	+	+	7.79	6.28	80.6	0.56	7.2	5.72	73.4	0.28	3.6	0.02	0.3	0.15	1.9	1.06	13.6		9.1	103.2
19	1000	1016	neutr.	O	O	7.71	6.68	86.6	0.48	6.2	6.20	80.4	0.24	3.1	0.13	1.7	0.13	1.7	0.53	6.9		7.8	101.4
20	1800	1009	acid	O	++	9.85	8.07	81.9	0.39	4.0	7.68	77.9	0.26	2.6	0.28	2.8	0.22	2.2	1.02	10.5		8.5	102.2
21	850	1020	acid	O	O	11.08	9.25	83.5	0.59	5.3	8.66	78.2	0.23	2.1	0.36	3.2	0.23	2.1	1.01	9.1		7.5	102
22	1665	1008	acid	O	+	7.97	6.41	80.4	0.50	6.3	5.91	74.1	0.23	2.9	0.07	0.9	0.17	2.1	1.09	13.7		7.5	101
23	1100	1013	acid	+	+++	8.50	6.70	78.8	0.52	6.1	6.18	72.7	0.26	3.2	0.24	2.9	0.20	2.4	1.10	12.7		8.5	100
24	1305	1010	acid	+	+++	7.91	6.45	81.5	0.43	5.4	6.02	76.1	0.18	2.3	0.13	1.6	0.20	2.5	0.95	12.1		5.9	100.5
25	1455	1010	acid	+	+	8.37	6.85	81.8	0.65	7.8	6.20	74.0	0.29	3.5	0.13	1.6	0.23	2.7	0.87	10.4		9.4	101
26	1005	1013	acid	O	+	6.63	5.44	82.1	0.44	6.6	5.00	75.5	0.18	2.7	0.14	2.1	0.18	2.7	0.69	10.4		5.9	100
27	1009	1009	alk.	O	++	7.06	5.90	83.6	0.66	9.4	5.24	74.2	0.26	3.7	0.12	1.4	0.17	2.4	0.61	8.9		8.5	101
28	1460	1013	amph.	O	+	10.82	9.06	83.7	0.47	4.3	8.59	79.4	0.38	3.5	0.00	0.0	0.28	2.6	1.10	10.2		12.3	99.5
29	1645	1010	alk.	O	+	7.60	6.17	81.2	0.49	6.4	5.68	74.8	0.28	3.7	0.07	0.9	0.18	2.4	0.90	11.8		9.1	98
30	1565	1009	alk.	+	+	6.84	5.47	80.0	0.36	5.3	5.11	74.7	0.25	3.7	0.00	0.0	0.14	2.0	0.98	14.3	27.2	9.1	100
31	1250	1009	alk.	+	O	5.57	4.64	83.3	0.39	7.0	4.25	76.3	0.25	4.5	0.00	0.0	0.13	2.3	0.55	9.9		9.1	99
32	1740	1009	alk.	O	O	7.50	6.16	82.1	0.52	6.9	5.64	75.2	0.31	4.1	0.00	0.0	0.19	2.5	0.84	1.13		11.4	99.6

33	1765	1008	alk.	O	+	8.45	7.07	83.9	0.53	6.3	6.56	77.6	0.35	4.1	0.00	0.0	0.22	2.6	0.79	9.4		12.8	99.4
34	1325	1009	alk.	O	+	6.04	5.05	83.6	0.38	6.3	4.67	77.3	0.27	4.5	0.00	0.0	0.14	2.3	0.58	9.6		9.9	100
35	1225	1012	alk.	O	+	6.21	5.26	84.7	0.47	7.6	4.79	77.1	0.27	4.3	0.00	0.0	0.17	2.7	0.51	8.3		9.9	100
37	1040	1015	acid	+	+++	8.84	8.32	94.1	0.52	5.9	7.80	88.2	0.19	2.2	0.00	0.0	0.09	1.0	0.24	2.7		6.9	103
38	1330	1012	acid	+	++	7.06	5.97	84.6	0.39	5.5	5.58	79.1	0.28	4.0	0.00	0.0	0.13	1.8	0.68	9.6		10.2	101
39	745	1012	acid	O	+++	6.00	3.78	63.0	0.22	3.6	3.56	59.4	0.19	3.2	0.13	2.2	0.16	2.7	1.74	28.9		6.9	102
40	1145	1011	alk.	+	+	5.29	3.58	67.7	0.29	5.5	3.29	62.2	0.23	4.3	0.07	1.3	0.14	2.7	1.27	24.0	27.8	8.2	101.5
41	2025	1008	acid	O	+	7.45	6.40	85.9	0.77	10.3	5.63	75.6	0.32	4.3	0.00	0.0	0.16	2.2	0.57	7.6		11.5	100
42	1320	1009	acid	+	+	5.60	4.75	84.8	0.45	8.0	4.30	76.8	0.26	4.6	0.00	0.0	0.14	2.5	0.45	8.1		9.3	100
43	1410	1010	alk.	O	+	5.17	4.46	86.3	0.27	5.2	4.19	81.1	0.27	5.2	0.00	0.0	0.11	2.1	0.33	6.4	27.2	9.9	100.5
44	1340	1008	alk.	O	+	5.37	4.06	75.6	0.40	7.4	3.66	68.2	0.21	3.9	0.00	0.0	0.12	2.2	0.98	18.3		7.7	101
45	1600	1009	alk.	O	+	6.32	5.60	88.6	0.54	8.5	5.06	80.1	0.22	3.5	0.00	0.0	0.13	2.1	0.37	5.8	28.0	7.8	100.5
46	1690	1010	alk.	O	+	6.76	5.92	87.6	0.51	7.5	5.41	80.1	0.26	3.8	0.00	0.0	0.15	2.2	0.43	6.4		9.2	100
47	1240	1009	alk.	O	+	4.85	4.26	87.8	0.43	8.9	3.83	78.9	0.21	4.4	0.00	0.0	0.12	2.5	0.26	5.3		7.5	100
48	1880	1008	alk.	O	+	6.00	5.26	87.7	0.39	6.5	4.87	81.2	0.24	4.0	0.00	0.0	0.14	2.3	0.36	6.0		8.5	99.5
49	1660	1009	acid	O	+	6.54	5.73	87.6	0.53	8.1	5.20	79.5	0.23	3.5	0.05	0.8	0.13	2.0	0.40	6.1		8.2	99.2
50	1420	1011	acid	O	+	7.13	6.19	86.8	0.60	8.4	5.59	78.4	0.28	3.9	0.04	0.6	0.14	2.0	0.48	6.7		10.0	99.4
51	1375	1010	acid	O	+	5.80	5.11	88.1	0.22	3.8	4.89	84.3	0.19	3.3	0.03	0.5	0.11	1.9	0.36	6.7		6.7	
52	745	1013	acid	O	+++	5.59	4.81	86.0	0.39	7.0	4.42	79.0	0.16	2.9	0.02	0.4	0.13	2.3	0.47	8.4		5.7	
53	1420	1007	acid	O	++	6.53	5.82	89.1	0.38	5.8	5.44	83.3	0.19	2.9	0.04	0.6	0.10	1.5	0.38	5.9		6.7	
54	1770	1008	acid	O	O	5.38	4.71	87.5	0.53	9.8	4.18	77.7	0.23	4.3	0.04	0.7	0.09	1.7	0.31	5.8	31.4	7.3	

the heat value to 456 calories. There was no marked change in the nitrogen content of the urine. On the twentieth day the patient received 7.06 gm. N and 1,034 calories. The nitrogen output was still 11.78 gm.

CASE 16.—*Patient.*—Male, aged 13, admitted to Bellevue Hospital, April 2, 1907, service of Dr. Alexander Lambert. During the seventeenth to twentieth days of the disease the patient was restless; on the twenty-first day comfortable; on the twenty-second day hungry. On the seventeenth day the blood gave a positive Widal reaction, and showed 5,000 leucocytes, of which 64 per cent. were polynuclear. The weight ran as follows: Seventeenth day, 67 pounds; thirtieth day, 60 pounds; thirty-ninth day, 62 pounds; forty-second day, 60 pounds; forty-fourth day, 64 pounds; fifty-third day, 70 pounds.

This case is one of a mild typhoid fever in a young boy. On the thirty-sixth day of the disease there was a mild relapse lasting about one week. It was attended by marked albuminuria and indicanuria. The total nitrogen rose slightly, the urea N fell from 88 per cent. to 59 per cent., kreatin reappeared, uric acid increased, and the rest N rose from 2.7 per cent. to 28.9 per cent.

Diet.—From the seventeenth to twenty-sixth days the patient received chicken broth, crackers and jelly, containing 3.0 gm. N and 218 calories. During this period there was a daily loss of N of about 4 gm. From the twenty-seventh to thirty-seventh days he received 5.5 gm. N and 789 calories. The nitrogen excretion then varied between 6 and 10 gm. Toward the end of the observations he received 6.8 gm. N and about 1,774 calories, while the nitrogen output ran between 5 and 7 gm. Before leaving the hospital he was placed on soft diet, of which the nitrogen and caloric value were not determined.

CASE 17.—*Patient.*—Man, aged 29; admitted to Bellevue Hospital April 3, 1907, service of Dr. Alexander Lambert. Weight, eleventh day, 117 pounds; thirty-sixth day, 112 pounds. The patient was at no time very sick, complaining chiefly of headache and neuralgic pains. Blood examination on the eleventh day showed 6,800 leucocytes, Widal positive; culture positive. The chief point of interest is the slight change in the nitrogen metabolism and the mild symptoms. Nevertheless there was a mild relapse covering the forty-third to fifty-sixth days.

Diet.—From the twelfth to the twenty-third days of the disease the patient received a diet of crackers, jelly and chicken broth, containing 3.2 gm. N and 219 calories. From the twenty-third to thirtieth days rice was added, making 4.94 gm. N and 640 calories. The output at this time was 10.8 to 14 gm. N.

CASE 18.—*Patient.*—Man, aged 29, weight 155 pounds, admitted to Bellevue Hospital April 8, 1907, service of Dr. Alexander Lambert. On the sixth day patient complained of severe headache, difficult urination, and took very little food. Definite improvement began on the eighth day.

This case presents the termination of a rather severe attack of typhoid fever. The chief point of interest is the high total nitrogen of the sixth day, with normal partition. In the third week sharp increases in the rest nitrogen were associated with increasing albuminuria and high indicanuria.

Diet.—From the sixth to eleventh days he received arrowroot jelly, rice, butter and chicken broth, containing 2.8 gm. N and 1,671 calories, including 720 calories in butter. On the seventh day he eliminated 33.6 gm. N, a net loss for that day of 30 gm., equal to 900 gm. of muscle tissue. During the rest of this period he excreted in the urine 16 to 20 gm. N daily. From the fourteenth to twenty-third days he was given hominy and chicken broth, containing 2.5 gm. N and 425 calories. The nitrogen output during this period fell to 8.6 gm.

CASE 19.—*Patient.*—Woman, aged 35. Illness began acutely six days before admission to New York Hospital, service of Dr. Conner, Aug. 12, 1908. The patient ran through a very severe attack of typhoid fever, the temperature reaching 104 F. or above from the seventh to eighteenth day, declining abruptly on the twenty-first day. During the febrile period there were constant delirium or

TABLE 7.—URINARY ANALYSES, CASE 17

Day of Disease.	Volume c.c.	Sp. Gr.	Reaction.	Albumin.	Indican.	Total N. Gm.	Gross Urea N.		NH_3 N.		Urea N.		Kreatinin N.		Kreatin N.		Uric Acid N.		Rest N.		Temp.
							Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	
12	890	1025	acid	+	++	16.68	14.31	85.8	0.61	3.7	13.70	82.1	0.75	4.5	0.25	1.5	0.28	1.7	1.09	6.5	103.2
13	890	1024	acid	+	+	13.79	12.03	87.2	0.52	3.8	11.51	83.4	0.38	2.8	0.11	0.8	0.18	1.3	1.09	7.9	103.2
14	1420	1017	acid	+	+	16.75	14.06	83.9	0.40	2.4	13.66	81.5	0.64	3.8	0.11	0.7	0.34	2.0	1.60	9.6	103.2
15	1600	1015	acid	O	O	16.27	13.76	84.6	0.80	4.9	12.96	79.7	0.61	3.7	0.18	1.1	0.30	1.8	1.42	8.8	103.4
16	1670	1013	acid	+	+	14.35	12.06	84.0	0.68	4.8	11.38	79.2	0.43	3.0	0.27	1.9	0.28	2.0	1.31	9.1	103.2
17	1350	1017	acid	O	+	17.15	14.68	85.6	0.71	4.1	13.97	81.5	0.61	3.6	0.15	0.9	0.36	2.1	1.35	7.8	103
18	1245	1015	acid	+	+	12.82	10.46	81.6	0.51	4.0	9.95	77.6	0.17	1.3	0.23	1.9	0.26	2.0	1.70	13.2	103.6
19	1665	1013	acid	+	+	14.45	12.23	84.6	0.65	4.5	11.58	80.1	0.43	3.0	0.13	0.9	0.33	2.3	1.33	9.2	102.2
20	1285	1018	acid	+	+	16.35	13.78	84.3	0.76	4.6	13.02	79.7	0.53	3.0	0.23	1.4	0.39	2.4	1.42	8.7	102
21	1920	1013	acid	+	+	15.38	13.40	87.1	0.63	4.1	12.77	83.0	0.54	3.5	0.15	1.0	0.32	2.1	0.97	6.3	101.4
22	1620	1013	acid	+	+	14.31	12.40	86.7	0.68	4.8	11.72	81.9	0.47	3.3	0.00	0.0	0.29	2.0	1.15	8.0	102
23	1915	1012	acid	+	O	14.61	12.20	83.5	0.75	5.1	11.45	78.4	0.50	3.4	0.00	0.0	0.31	2.1	1.60	11.0	100
24	2035	1011	acid	+	+	14.01	11.97	85.4	0.77	5.5	11.20	79.9	0.47	3.4	0.00	0.0	0.26	1.9	1.31	9.3	102
25	2030	1011	acid	+	+	12.98	10.74	82.7	0.77	5.9	9.97	76.8	0.49	3.8	0.00	0.0	0.28	2.2	1.47	11.3	101.2
26	2500	1008	acid	+	O	12.67	10.80	85.2	0.75	5.9	10.05	79.3	0.50	3.9	0.00	0.0	0.30	2.4	1.07	8.5	99.6
27	1745	1010	acid	+	+	11.13	9.47	85.1	0.66	5.9	8.81	79.2	0.40	3.6	0.00	0.0	0.28	2.5	0.98	8.8	101.2
28	1755	1011	acid	+	+	11.28	9.28	82.3	0.68	6.0	8.60	76.3	0.42	3.7	0.00	0.0	0.30	2.7	1.28	11.3	101.2
29	2220	1008	acid	+	+	10.79	9.35	86.6	0.84	7.8	8.51	78.8	0.44	4.1	0.00	0.0	0.27	2.5	0.73	6.8	100
30	1805	1012	alk.	+	+	10.81	8.97	83.0	0.74	6.8	8.23	76.2	0.47	4.3	0.00	0.0	0.27	2.5	1.10	10.2	100
31	3525	1008	acid	O	+	11.98	10.00	83.5	0.99	8.3	9.01	75.3	0.56	4.7	0.00	0.0	0.35	2.9	1.07	8.9	100
32	2270	1008	acid	+	+	10.98	9.53	86.8	0.39	3.5	9.14	83.3	0.41	3.7	0.00	0.0	0.36	3.3	0.66	6.2	98.4

TABLE 8.—URINARY ANALYSES, CASE 18

Day of Disease.	Volume c.c.	Sp. Gr.	Reaction.	Albumin.	Indican.	Total N. Gm.	Albumin N. Gm.	Gross Urea N.		NH_3 N.		Urea N.		Kreatinin N.		Kreatin N.		Uric Acid N.		Rest N.		Temp.
								Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	
6	1534	1028	acid	++	+	33.65	....	28.80	85.6	0.80	2.4	28.00	83.2	0.38	1.1	1.00	3.0	0.46	1.4	3.01	8.9	103
7	975	1024	acid	++	+++	19.35	....	15.90	82.2	0.68	3.5	15.22	78.7	0.58	3.0	0.16	0.8	0.31	1.6	2.40	12.4	103.4
8	1165	1021	acid	++	+	20.29	....	17.41	85.8	0.59	2.9	16.82	82.9	0.65	3.2	0.42	2.1	0.43	2.1	1.38	6.8	103
9	1160	1017	acid	+	++	16.95	....	14.41	85.0	1.06	6.3	13.35	78.7	0.68	4.0	0.00	0.0	0.35	2.1	1.51	8.9	102.4
10	810	1020	acid	+	+	14.05	....	11.80	84.0	0.59	4.2	11.21	79.8	0.15	1.1	0.23	1.6	0.31	2.2	1.56	11.1	103
11	925	1020	acid	+	+	16.50	....	14.00	84.8	0.65	3.9	13.35	80.9	0.57	3.5	0.13	0.8	0.42	2.5	1.38	8.4	101
12	985	1020	acid	+	++	16.20	....	13.59	83.9	0.69	4.3	12.90	79.6	0.65	4.0	0.10	0.6	0.41	2.5	1.45	9.0	101.4
13	1540	1015	acid	+	+	17.35	....	14.86	85.7	0.89	5.1	13.97	80.6	0.66	3.8	0.00	0.0	0.42	2.4	1.41	8.1	101
14	940	1017	acid	+	0	11.58	....	9.88	85.3	0.29	2.5	9.59	82.8	0.43	3.7	0.00	0.0	0.29	2.5	0.98	8.5	101
15	1950	1012	acid	+	++	17.14	....	14.21	82.9	0.70	4.1	13.51	78.8	0.74	4.3	0.16	0.9	0.45	2.6	1.58	9.3	100.5
16	1125	1015	acid	+++	+	11.30	0.88	9.28	89.1	0.45	4.3	8.83	84.8	0.51	4.9	0.06	0.6	0.31	3.0	0.26	2.4	101
17	1110	1011	acid	+++	++	8.60	0.65	6.93	82.7	0.34	4.3	6.59	82.9	0.37	4.5	0.08	1.0	0.25	3.1	0.32	4.2	100.5
18	1700	1013	acid	+++	+	15.64	0.14	12.88	83.0	0.34	2.2	12.54	80.8	0.36	2.3	0.07	0.5	0.41	2.7	1.78	11.5	99.5
19	1260	1017	acid	+++	++	13.45	0.43	11.29	86.7	0.48	3.7	10.81	83.0	0.60	4.6	0.19	1.5	0.35	2.7	0.59	4.5	99
20	770	1019	acid	+	+	9.69	....	8.45	87.3	0.20	3.0	8.16	84.3	0.45	4.5	0.12	1.2	0.24	2.5	0.43	4.5	99

TABLE 9.—URINARY ANALYSES, CASE 19

Day of Disease.	Volume c.c.	Sp. Gr.	Reaction.	Total N. Gm.	Gross Urea N.		NH_3 N.		Urea N.		Kreatinin N.		Kreatin N.		Uric Acid N.		Rest N.		Temp.	Kreatinin Coefficient.
					Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%		
20	325	1018	acid	4.29	3.46	80.8	0.224	5.24	3.23	75.6	0.228	5.34	0	....	0.065	1.5	0.529	12.3	102.8	5.4
21	300	1021	acid	3.50	2.96	87.3	0.122	3.49	2.84	81.1	0.212	6.05	0	....	0.02	0.59	0.304	8.7	104.8	5.0
22	250	1023	acid	3.29	2.88	87.3	0.092	3.2	2.77	84.1	0.17	5.1	0	....	0.015	0.46	0.232	7.0	99	4.9
23		Urine Lost																		
24	265	1017	acid	2.81	2.40	85.6	0.098	3.4	2.30	82.1	0.186	6.6	0	....	0.018	0.66	0.201	7.1	101.2	4.5
25	300	1022	acid	3.19	2.82	88.1	0.091	2.8	2.73	85.3	0.24	7.5	0	....	0.021	0.67	0.116	3.6	101	6.0
26	315	1023	acid	4.04	3.09	76.3	0.148	7.6	2.93	72.7	0.21	5.2	0	....	0.063	1.6	0.683	16.8	98.6	5.0
27	300	1020	acid	3.70	2.90	78.7	0.19	5.1	2.71	73.6	0.216	5.8	0	....	0.014	0.39	0.588	15.04	98.2	5.2
28	320	1022	acid	3.46	2.94	84.3	0.17	4.9	2.77	79.4	0.217	6.2	0	....	0.013	0.39	0.316	9.06	100.2	5.4
29	300	1020	acid	2.74	2.20	80.2	0.14	5.1	2.06	75.1	0.19	6.9	0.013	0.47	0.02	0.73	0.319	11.6	100.2	4.7
30	300	1020	acid	3.33	2.58	77.9	0.17	5.0	2.42	72.8	0.2	6.0	0.024	0.72	0.06	1.86	0.452	13.5	98.2	4.9
31	265	1020	acid	3.25	2.57	79.3	0.19	5.8	2.39	73.5	0.18	5.4	0.021	0.65	0.034	1.04	0.442	13.6	98	4.6
32	310	1024	acid	3.75	2.99	79.8	0.20	5.3	2.79	74.5	0.214	5.7	0.009	0.24	0.045	1.20	0.491	13.0	98.6	5.0
33	300	1018	acid	3.29	2.69	81.4	0.18	5.5	2.51	75.9	0.20	6.1	0	....	0.06	1.9	0.347	10.5	98.6	4.9
34	275	1020	acid	3.18	2.58	81.4	0.22	7.0	2.36	74.4	0.2	6.3	0	....	0.09	2.8	0.3	9.4	98.4	4.9
35	295	1019	acid	3.18	2.58	81.0	0.21	6.6	2.37	74.4	0.2	6.5	0	....	0.079	2.5	0.32	10.0	99	4.9
36	290	1016	acid	2.37	1.87	79.3	0.22	9.0	1.66	70.2	0.2	7.0	0	....	0.021	0.9	0.3	12.7	98.4	4.9
37	305	1022	acid	3.29	2.38	72.4	0.32	9.7	2.06	62.7	0.2	6.1	0	....	0.018	0.55	0.69	20.9	98.6	4.9
38	295	1013	acid	2.56	1.91	74.6	0.24	9.1	1.67	65.4	0.18	7.0	0	....	0.06	2.5	0.4	15.8	98.6	4.6
47	?	1012	acid	?	?	77.4	?	8.7	?	68.7	?	5.0	0	....	?	1.71	?	15.8	98.6	
48	305	1011	acid	2.11	1.59	75.4	0.19	9.1	1.4	66.3	0.14	6.6	0	....	0.031	1.48	0.347	16.4	99.0	3.4
49	570	1008	acid	3.46	2.82	81.4	0.35	10.0	2.47	71.4	0.19	5.3	0	....	0.016	0.46	0.44	12.7	98.0	4.6

stupor, frequent vomiting, rapid emaciation and incontinence of urine. Several blood cultures were negative. Widal positive. Lumbar punctures were several times performed on account of meningeal symptoms.

On account of vomiting and stupor the patient received very little nourishment, and toward the end of the febrile period was in a state of almost complete starvation, the stomach retaining nothing. After defervescence, delirium, vomiting and incontinence continued and the patient remained in a very critical condition. About the twenty-sixth day the temperature fell, there was some slight improvement in the pulse and mental condition, and incontinence ceased, but the patient still refused food or vomited most of that ingested. At this time the weight was 89 pounds. After the twenty-sixth day the patient began to retain some pasteurized milk. On the thirty-seventh day 100 gm. of chicken, 60 gm. bread, 25 gm. butter and 55 gm. egg were taken (N, 4.91 gm.; calories, 596) and similar food was offered thereafter, but was partly refused or vomited. The observations terminated when the patient, in a very weak condition, weighing 94 pounds, was taken to the country. She eventually recovered. Although extreme care was observed it was found impossible, using the catheter every 4 to 6 hours, to collect all the urine, small portions of which were frequently lost. Yet the portions lost were carefully estimated and were not large, so that the total amount obtained on days when none was lost did not vary greatly from that of other days, and constant relative anuria clearly existed. While realizing that this deficiency vitiates the observations on total nitrogen, we do not believe the error from this source to be large.

With this reservation we may note several interesting features in this case. First, a state of advanced starvation existed toward the end of the febrile period, during which, with very low total N, the urea N remained unusually high and the ammonia N and the rest N relatively low, suggesting that the presence of fever may eliminate the usual features of the nitrogen partition of starvation. Second, a considerable rise in the ratio of urea N during the twentieth to twenty-second days indicated an improvement in metabolism in spite of a sharp exacerbation of fever, this improvement heralding a rapid defervescence. Third, the steady decline in urea N ratio and rise in the ammonia N during convalescence suggests the appearance of starvation acidosis. Fourth, the striking increase in the rest N on the thirty-seventh day followed the addition to the diet of meat and eggs and suggests that the organism was unable to metabolize properly the products of digestion of this rich protein food. At the same time the pulse was accelerated 15 to 20 beats, the temperature rose 2° on the thirty-ninth and fortieth days, and the patient was less comfortable and vomited occasionally.

Case 20.—*Patient.*—Woman, aged 20, weight on fifty-ninth day, 78 pounds; admitted on the fifteenth day of disease to New York Hospital, service of Dr. Conner, Aug. 29, 1908. The patient ran through a very severe attack of typhoid fever, complicated by extensive hemorrhages. The temperature from the fifteenth to the twenty-second day reached 104 to 105 F., falling during the days of hemorrhage (nineteenth and twentieth of illness). After a short remission on the twenty-fourth day it rose again and continued above 104 until the present observations began, when its course is indicated in the table. Incessant vomiting nullified all attempts at feeding. Two large hemorrhages reduced the hemoglobin to 30 per cent. and left the patient in a critical condition for several days. The return of fever was accompanied by vomiting, excessive tympanites, a very low nervous state, repeated small bleedings with involuntary stools, and consolidation of the lower lobe of right lung, twenty-seventh day.

At the beginning of the urinary analyses the patient was taking very little nourishment, vomited occasionally, and was extremely feeble. The pulse did not fall to 100 until the forty-sixth day. On the thirty-second to thirty-fourth days she retained a little barley water; on the thirty-third day 50 gm. of lactose were

TABLE 10.—URINARY ANALYSES, CASE 20

Day of Disease.	Volume.	Sp. Gr.	Reaction.	Albumin.	Indican.	Total N. Gm.	Gross Urea N.		NH_3 N.		Urea N.		Kreatinin N.		Kreatin N.		Uric Acid N.		Rest N.		Temp.
							Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	
32	1575	1003	acid	+	+	5.37	4.07	75.9	0.53	9.9	3.53	66.0	0.25	4.6	0.106	2.0	0.117	2.2	0.868	15.3	103.6
33	1440	1004	acid	++	O	4.83	3.92	80.9	0.29	8.0	3.52	72.9	0.188	3.9	0.199	4.1	0.161	3.3	0.372	7.7	102.6
34	1145	1005	acid	+	O	4.81	3.78	78.6	0.33	6.7	3.45	71.8	0.146	3.0	0.167	3.5	0.085	1.8	0.633	13.1	102.8
35	2096	1002	acid	O	O	4.82	3.98	82.5	0.44	9.1	3.54	73.4	0.21	4.3	0.18	3.7	0.08	1.7	0.37	7.7	102
36	1280	1004	acid	O	O	3.58	2.53	70.7	0.26	7.3	2.27	63.4	0.15	4.0	0.099	2.7	0.05	1.4	0.757	21.2	103.4
37	1100	1007	acid	+	O	4.82	3.08	64.0	0.155	3.2	2.93	60.8	0.21	4.3	0.185	3.8	0.065	1.3	1.28	26.5	101.2
38	1125	1004	acid	+	++	*	....	74.4	.....	12.3	....	62.1	.....	4.9	.....	4.0	.....	2.8	.....	13.8	100.4
39	910	1005	acid	++	++	3.71	2.63	71.0	0.43	11.5	2.21	59.5	0.19	5.0	0.27	7.3	0.1	2.7	0.51	13.8	100.6
40	770	1004	acid	O	++	3.49	2.69	77.0	0.5	14.5	2.18	62.5	0.15	4.2	0.155	4.4	0.1	3.1	0.388	11.2	101
41	600	1010	acid	+	O	4.24	3.24	76.4	0.47	11.0	2.77	65.3	0.19	4.4	0.111	2.6	0.127	3.0	0.575	13.5	100.8
42	700	1005	acid	+	O	*	....	75.7	.....	13.2	....	62.5	.....	3.7	.....	3.8	.....	2.4	.....	14.3	100.2
43	700	1007	alk.	+	O	3.21	2.51	78.3	0.57	17.8	1.94	60.5	0.13	3.9	0.104	3.2	0.084	2.6	0.384	12.1	100.2
44	970	1003	acid	O	O	3.88	3.23	83.2	0.262	6.7	2.97	76.5	0.18	4.7	0.025	0.6	0.087	2.2	0.355	9.1	99.6
45		?				*															
46	350	1016	acid	O	++	2.81	2.24	79.3	0.301	10.6	1.94	68.6	0.143	5.0	0.011	0.4	0.092	3.2	0.344	12.0	99.8
47	400	1023	acid	O	O	4.51	3.52	77.8	0.414	9.1	3.10	68.7	0.184	4.0	0.014	0.3	0.16	3.5	0.645	14.2	99.8
48	555	1016	acid	O	++	4.35	3.51	80.7	0.40	9.2	3.11	71.5	0.164	3.7	0.053	1.2	0.12	2.7	0.501	11.5	99.8
49	650	1013	acid	O	O	4.05	3.20	79.2	0.292	7.2	2.91	72.0	0.156	3.8	0.025	0.6	0.087	2.1	0.575	14.1	99.8
50	750	1014	acid	O	O	4.56	3.81	83.6	0.48	10.5	3.34	73.1	0.176	3.8	0.022	0.5	0.115	2.5	0.436	9.5	99.2

* Incomplete.

TABLE 11.—URINARY ANALYSES, CASE 21

Day of Disease.	Volume.	Sp. Gr.	Albumin N.		Total N., Gm.	Gross Urea N.		NH_3 N.		Urea N.		Kreatinin N.		Kreatin N.		Uric Acid N.		Rest N.		Indican.	Reaction.	Temp.
			Gm.	%		Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%			
7	562	1028	1.600	13.7	10.1	8.7	86.14	0.764	7.56	7.94	78.58	0.421	4.17	0.073	0.72	0.135	1.34	0.77	7.63	+++	acid	104.8
8	650	1024	1.8	13.64	11.3	9.9	87.56	1.03	9.18	8.43	78.38	0.47	4.12	0.067	0.59	0.137	1.21	0.745	6.52	++	acid	104.4
9	500	1023	0.46	4.8	8.23	6.3	82.4	0.637	7.7	6.16	74.7	0.257	3.12	0.143	1.73	0.112	1.36	0.938	11.39	O	acid	103.0
10	720	1011	0.44	6.69	6.13	5.05	82.4	0.756	12.32	4.29	70.08	0.317	5.17	0.180	2.93	0.16	2.61	0.422	6.89	O	acid	101.8
11	1365	1004	0.068	0.96	7.03	5.73	81.5	0.75	10.67	4.98	70.83	0.32	4.56	0.212	3.01	0.158	2.25	0.609	8.68	+	alk.	101.6
12	1775	1005	0.21	2.963	7.01	5.66	81.0	0.505	7.2	5.17	73.8	0.422	6.02	0.18	2.57	0.185	2.64	0.542	7.77	O	acid	102
13	1215	1007	Trace	.....	6.56	5.42	81.46	0.62	9.27	4.8	72.19	0.4	6.0	0.157	2.36	0.16	2.5	0.51	7.68	O	acid	101.4
14	1375	1005	Trace	.....	5.88	4.00	81.8	0.413	8.46	3.58	73.34	0.29	5.92	0.165	3.38	0.055	1.13	0.38	7.77	+	acid	101.4
15	1475	1004	Trace	.....	4.84	3.84	79.28	0.398	8.22	3.43	71.04	0.288	5.95	0.059	1.22	0.05	1.05	0.607	12.52	+	acid	100.2

TABLE 12.—URINARY ANALYSES, CASE 22

Day of Disease.	Volume c.c.	Sp. Gr.	Reaction.	Total N., Gm.	N., Gm. Albumin.	Gross Urea N.		Amm. N.		Urea N.		Kreatinin N.		Kreatin N.		Uric Acid N.		Rest N.		Pulse.	Temp.	General Condition.
						Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%			
23	2700	1015	acid	29.70	0.783	25.650	88.70	1.296	4.48	24.354	84.22	0.459	1.59	0.173	0.60	0.364	1.26	2.271	7.85	124	102.4	Apathy incontinent.
24	2840	1015	acid	28.90	0.815	23.850	84.90	1.221	4.35	22.629	80.55	0.496	1.77	0.072	0.26	0.227	0.81	3.440	12.26	124	102.8	Brighter.
25	1430	1017	acid	14.910	0.470	12.725	88.10	0.721	4.99	12.004	83.11	0.236	1.63	0.080	0.55	0.157	1.09	1.242	8.63	116	102.0	Subsultus.
26	2042	1016	acid	21.885	0.245	18.620	86.00	1.154	5.30	17.466	80.70	0.384	1.78	0.065	0.30	0.278	1.28	2.293	10.64	120	102.0	Brighter; restless.
27	1600	1016	acid	16.605	0.285	13.470	82.54	0.896	5.49	12.574	77.05	0.341	2.09	0.059	0.36	0.282	1.73	2.168	13.28	110	101.6	Brighter; restless.
28	1530	1017	acid	15.637	0.215	13.005	84.30	0.880	5.71	12.125	78.59	0.298	1.93	0.028	0.18	0.230	1.50	1.861	12.09	116	102.4	Much better; hungry.
29	1550	1016	acid	15.035	0.155	12.137	81.54	1.015	6.80	11.122	74.74	0.279	1.87	0.078	0.52	0.220	1.47	2.174	14.60	120	99.0	Improving.

Diet: Twenty-third to twenty-ninth day, milk 50 oz., lactose 500 gm., N. 7.7 gm., Cal. 3368.

given but vomited; on the thirty-fourth day 75 gm. of lactose (300 calories) were retained. On the thirty-fifth day she took scraped beef 1 ounce, beef juice 0.5 ounce and 190 gm. lactose (N, 1 gm.; calories, 785), and on the thirty-sixth day one egg; ice cream, 6 ounces; broth, 6 ounces; toast, 25 gm.; beef juice, 2 ounces; lactose, 125 gm. (N 1.8 gm.; calories, 910). Thereafter a somewhat similar diet was maintained under which very slow improvement began. Discharged cured, seventy-fifth day.

In this case our observations cover the terminal febrile period and beginning convalescence of a remarkably severe typhoid fever. During the entire period the patient was reduced to an extremely low state of vitality, in which typhoid intoxication, pneumonia, anemia and starvation were combined. The very low total nitrogen we refer to this general condition. On account of incontinence the urine was drawn by catheter. The first analysis gave low urea, considerable ammonia and rather high rest nitrogen, which accord with the usual findings of severe febrile stages of typhoid fever. The later fall in urea we are inclined to refer in part to starvation acidosis. On the thirty-fifth day the addition to the diet of scraped beef and beef juice was followed by a striking increase in the rest N, indicating, as in Case 19, that the organism was unable to metabolize the products of digestion of this protein food. The considerable excretion of kreatin accords with the extreme loss of flesh. As improvement set in the kreatin diminished.

CASE 21.—*Patient.*—Woman, aged 38, weight on twenty-ninth day 107 pounds, admitted Oct. 1, 1908, to New York Hospital, service of Dr. Conner. The patient ran through a typical sharp attack of typhoid fever lasting 28 days. The chief feature was the temperature, which reached 104.2° on the third day, and remained constantly between 104° and 106° until the eighth day. There was rapid loss of flesh, considerable diarrhea and abdominal pain but no grave symptoms. The diet consisted of small quantities of meat broth, custard, gelatin and lactose. Beginning on the fifth day, 75 to 100 gm. of lactose were given; on the eighth day, 115 gm.; ninth to eleventh days, 45 gm.; twelfth day, 70 gm.; thereafter about 200 gm. On the thirteenth day the estimated calories of the diet were 2,064, which was maintained. The patient made a quick recovery.

The urinary analyses show a high gross urea ratio, low rest N and very favorable course, notwithstanding the high fever. The low total N may be referred to the carbohydrate diet which was instituted at the suggestion of Dr. Conner to test the influence of this diet on the course of typhoid fever. In spite of this diet the ammonia N reached or possibly exceeded the upper limits of a normal standard. The indican was unusually low. The albuminuria was partly the result of menstruation, but most of the urine was drawn by catheter.

CASE 22.—*Patient.*—Man, aged 26, admitted to House of Relief, service of Dr. Conner, Feb. 19, 1909, on the eleventh day of the disease. The patient passed through a very severe attack of typhoid fever, the temperature for twenty-four days remaining between 101 and 105° F. Constant apathy or stupor, incontinence, subsultus were present until the twenty-fourth day, when the patient improved slightly. Recovery was then rapid, but convalescence was interrupted by cystitis and multiple arthritis, which were attributed to the catheterizations. On the forty-ninth day he weighed 115 pounds.

The striking features of this case were the maintenance of a very high urea ratio during severe stages of the disease, and the prompt recovery. Throughout the disease the patient took nourishment well. From the eleventh to twenty-second days the diet consisted of milk, 60 ounces and lactose 300 gm (N, 9.3 gm.; calories, 2,350). Thereafter the diet was maintained as indicated in the table. To Dr. T. F. Laurie, house physician, we are indebted for very careful supervision of the case during the period of observation.

NOTE.—In addition to the articles cited in the text, the following may be consulted: Ewing: Proc. Philadelphia Path. Soc., 1905, new series, viii, 65. New York Med. Record, 1907, lxxi, 537.

A STUDY OF THE MECHANICAL FACTORS IN EXPERIMENTAL ACUTE PULMONARY EDEMA*

JOSEPH L. MILLER, M.D., AND S. A. MATTHEWS, M.D.

CHICAGO

During recent years the rôle of chemical agents in the development of edema has received considerable attention and several theories have been propounded with a view of explaining all forms of edema on a chemical basis. As a consequence the importance of mechanical factors has been somewhat discredited. Previous studies of the mechanical agents in acute pulmonary edema would indicate that here the phenomena may be explained on a mechanical basis. A continuance of these studies might, therefore, be of interest in order to determine whether pulmonary edema the result of other means than those previously employed could be explained without the aid of chemical agents.

In an exhaustive article published in 1878, William H. Welch[1] made the first attempt to explain, on an experimental basis, the phenomena of acute pulmonary edema. Working with rabbits he determined that ligation of the thoracic aorta, in such a manner that the only outlet was the left carotid and left subclavian, produced uniformly in animals with strong hearts a marked pulmonary edema. In animals with presumably weak hearts, as shown by the failure to respond to a rise in the pulmonary blood pressure, edema did not occur. He also determined that pulmonary edema could be produced by marked constriction of the pulmonary vein or compression of the left ventricle to the extent that its capacity was reduced 75 per cent. He noted that all of these procedures caused a marked rise in pressure in the pulmonary artery, which he considered a very important factor in the development of edema. Welch formulated the results of his experimental work in the following words: "Mechanical edema is the result of a disproportion between the working power of the left ventricle and the right ventricle of such a character that, the resistance remaining the same, the left heart is unable to expel in a unit of time the same quantity of blood as the right heart." This explanation of pulmonary edema gave as the important factor passive congestion in the pulmonary artery. Welch's theory called forth consid-

*From the Laboratory of Experimental Therapeutics, University of Chicago.

1. Welch, W. H.: Zur Pathologie des Lungenödems. Virchow's Arch. f. path. Anat., 1878, lxxii, 375.

erable criticism, especially from clinicians who attempted to apply this explanation to acute pulmonary edema in man. Sahli called attention to the absence of evidence of intense hyperemia in pulmonary edema, especially in nephritic and cachectic conditions. Welch answers this criticism by saying that the color of dropsical tissues is an unsafe guide as to their blood content, as a pale dropsical lung may be markedly hyperemic. Especial stress has been laid on the character of the pulse during an attack. While usually small and rapid, it is at times normal or even of high tension (Sahli,[2] Hewlett,[3] Riesman,[4] Crummer[5]). The presence of high pressure has been used as an argument against impaired activity of the left ventricle. Welch's reply to this criticism was that complete paralysis of the left ventricle is not necessary to cause a disproportion between the working power of the two ventricles.

Welch's experiments were repeated by Mayer,[6] Sahli[2] and Löwit.[7] Mayer obtained the same results, but considered the rise in systemic pressure to be due to vascular spasm excited by the cerebral anemia. Sahli, working with dogs instead of rabbits, was able only infrequently to produce edema, which he explained by the greater permeability of the vessel walls in rabbits, and this factor rather than mechanical agents he considers responsible for the edema. Löwit, in repeating the experiments, obtained the same results, but considers overfilling of the pulmonary vessels as an important element. By taking the pressure in the left auricle and at the same time in the pulmonary and systemic circulation, he made the interesting observation that an increase in the pulmonary artery may be associated with lessened pressure in the left auricle or *vice versa;* that is, that direct transmission of pressure through the pulmonary artery to the pulmonary vein does not necessarily occur.

Both Löwit and Bettelheim[8] were able to produce pulmonary edema by ligating the left coronary artery, the edema being associated with a fall in the systemic and a rise in the pulmonary pressure.

---

2. Sahli, H.: Zur Pathologie und Therapie des Lungenödems. Arch. f. exper. Path. u. Pharmakol., 1885, xix, 431.

3. Hewlett, H. M.: Four cases of acute suffocative pulmonary edema. Intercolonial Med. Jour., Australasia, 1903, viii, 611.

4. Riesman, D.: Acute pulmonary edema, with special reference to a recurrent form. Tr. Assn. Am. Phys., 1906, xxi, 155.

5. Crummer, L.: Acute suffocative pulmonary edema. Northwestern Lancet, 1902, xxii, 203.

6. Mayer, S.: Verhandl. d. Akad. d. Wissench, Wien., 1878, lxxvii, 266.

7. Löwit, M.: Ueber die Entstehung des Lungenödems. Beitr. z. path. Anat. u. z. allg. Path., 1893, xiv, 401.

8. Bettelheim, J.: Ueber die Störungen der Herzmechanik nach Kompression der Arteria Coronaria sinistra des Lungenödems. Ztschr. f. klin. Med., 1887, xii, 550.

Grossman[9] and Löwit produced pulmonary edema in dogs by intravenous injection of muscarin nitrate. Grossman reported a fall in the systemic pressure, with a temporary fall followed by a rise in the pulmonary artery. He explains these blood-pressure changes by a selective action of the drug causing spasm of the left ventricle. He calls attention, however, to a few instances in which the rise appeared earlier in the pulmonary artery than in the left auricle, a phenomenon which could not be explained by stasis in the left heart. As Brunton had stated that muscarin may constrict the pulmonary artery, Grossman cut the cord, but found that this did not interfere with the primary rise in the pulmonary artery. Brodie and Dixon[10] have recently shown that muscarin dilates rather than constricts the pulmonary artery. Löwit was able to produce pulmonary edema with muscarin. His results differ from Grossman in that almost invariably the rise in pressure appeared earlier in the pulmonary artery than in the left auricle and, therefore, stasis arising from spasm of the left ventricle could not be the cause. Grossman and Löwit agree that evidence of disproportion between the working power of the two sides of the heart develops, but that the cause of this disproportion is still undetermined. Muscarin edema has a direct clinical bearing as in poisoning with toadstools (*Agaricus muscarinus*) pulmonary edema is a prominent symptom. Pilocarpin, which resembles muscarin in its action, has probably been responsible for many attacks of pulmonary edema in nephritics. Tyson[11] refers to the frequency with which pulmonary edema appeared at the time it was customary to administer large doses of pilocarpin in kidney cases.

Löwit has studied very carefully the blood-pressure changes associated with acute pulmonary edema produced by acetic ether. He found, immediately after the intravenous injection of a small amount, a decided fall in the systemic blood pressure and simultaneously with this a rapid fall in the pressure in the pulmonary artery followed by cardiac standstill. Since these pressure changes do not show any evidence of stasis, Löwit considered that he had demonstrated that acute experimental pulmonary edema could be produced independently of mechanical agents. As supporting this view, he has been able to cause quite extensive transudation into the peritoneal cavity by the intraperitoneal injection of butyric ether.

---

9. Grossman, M.: Das Muscarin-Lungenödem. Ein Beitrag zur Lehre von der Entstehung des acuten Allgemeinen Lungenödems. Ztschr. f. klin. Med., 1887, xii, 550.

10. Brodie, T. G., and Dixon, W. E.: Contributions to the physiology of the lungs. Jour. Physiol., London, 1904, xxx, 476.

11. Tyson, J.: A discussion of Riesman's paper on acute pulmonary edema. Tr. Assn. Am. Phys., 1906, xxi, 175.

Guinard and Teisser[12] demonstrated typical pulmonary edema in rabbits after the intravenous injection of 30 mg. of methyl salicylate, the observed pressure changes corresponding to those seen after the use of muscarin.

Von Zeissl[13] by intravenous injection of Lugol's solution into dogs was able to produce very extensive pulmonary edema. During the development of the edema the pulmonary pressure always rose, the systemic pressure varied, at times a rise, at other times a fall, and, as had been observed with acetic ether, pressure changes in the left auricle that were apparently independent of that in the pulmonary artery. The right ventricle dilated, the left remained normal or became contracted. Although these pressure phenomena showed the presence of stasis, he considers changes in the vessel walls as probably an important factor in the development of the edema.

Finally, there is the experimental work of Powkusky[14] with carbonic oxid. He was able to cause extensive edema in dogs and rabbits by this means. Blood-pressure measurements were not made, but he reports that during the experiment the left side of the heart appeared empty and contracted, the right heart full and dilated and the pulmonary arteries distended with blood—precisely the appearance that had been noted after acetic ether and iodid.

Summarizing the cardiovascular changes observed in the pulmonary edema produced by these various chemical agents, we notice a striking similarity. Generally there is a fall in the systemic pressure and a rise in pressure in the pulmonary artery. At the same time the right side of the heart becomes dilated, the left remains normal in size or, as some have maintained, contracted. Pressure changes in the pulmonary artery are not necessarily associated with corresponding changes in the left auricle, since a rise in pressure in the pulmonary artery may be associated with a fall in pressure in the left auricle or *vice versa*.

EXPERIMENTAL OBSERVATIONS

Our experimental work was undertaken with a view of determining the following questions: first, whether acute pulmonary edema, produced by other agents than those already tried, is associated with a rise in

12. Guinard, S., and Teisser, J.: Nouvelles recherches expérimentales sur la pathogénie de l'oedème aigu du poumon. Jour. de physiol. et de path. gén., 1901, iii, 42.

13. Van Zeissl, M.: Ueber Lungenödem in Folge von Jodintoxication. Ztschr. f. klin. Med., 1895, xxvii, 363.

14. Powkusky, W.: Ueber die Vergiftung mit Kohlenoxydgas. Virchow's Arch. f. path. Anat., 1869, xxx, 524.

pressure in the pulmonary artery; second, to repeat the experiments with acetic ether, since in the previous work the acetic ether had been an exception, inasmuch as it produced pulmonary edema without an increase in pressure in the pulmonary artery; third, the value of various agents in controlling the development of modifying the course of acute experimental pulmonary edema.

Nitric oxid, ammonia vapors and illuminating gas are all recognized as causing acute pulmonary edema in man. Hall[15] reports three cases of edema in firemen exposed to the fumes of nitric oxid, and pulmonary edema under similar circumstances[16] has been noted with ammonia vapors. Adrenalin often produces a pulmonary edema in rabbits, and Sahli refers to the frequency with which pulmonary edema occurs in dogs poisoned by hydrocyanic acid. These various agents were employed in our work and, in addition, the effect of artificial mitral stenosis on the pulmonary circulation. Dogs were used in most of our experimental work. In a few cases rabbits were utilized instead. Ether was used as an anesthetic. Artificial respiration was maintained by a bellows and motor. The pressure in the pulmonary artery was determined by a mercury manometer, the descending arm of which had twice the diameter of the ascending arm; in this way slight changes in pressure could be more readily detected. The cannula was tied in the branch of the left pulmonary artery supplying the upper or middle lobe. The systemic pressure was taken from the right carotid. Pulmonary edema was considered present when froth either issued from the trachea or could be expressed freely from the large bronchi by moderate compression of the lung.

Nitric Oxid.—Nitric oxid was generated from a mixture of metallic copper and nitric acid. The fumes were forced from the flask in which they were generated into the tracheal tube, where they became mixed with the ether vapor. As soon as a small amount of the gas had been inhaled, there was a very decided fall in the carotid pressure with a very slight fall in pressure in the pulmonary artery. The carotid pressure soon reached a level at which it remained stationary, but the pressure in the pulmonary artery steadily continued to fall. If the amount of gas was suddenly increased, there was at once a fall in pressure in both arteries. Eight minutes after beginning the gas, bradycardia and arrhythmia were noted, followed by cardiac standstill. There was no evidence of unilateral dilatation of the heart at any time. The lungs

15. Hall, J. M., and Cooper, C. E.: The effects of inhalations of the fumes of nitric acid, with report of cases. Jour. Am. Med. Assn., 1905, xlv, 396.

16. Several cases of this character occurred in firemen fighting the flames in a refrigerator plant at the stockyards in Chicago.

showed very marked hemorrhagic edema; blood-tinged froth issued from the trachea. Here, as in all other edemas, the lower lobes were most extensively involved, the posterior median portion of the middle lobe less edematous, the remainder of the middle lobe still less involved. The upper lobes usually showed a slight patch in the posterior median portion. The lobe supplied by the branch of the pulmonary artery which contained the cannula was always free from edema.

The changes in blood pressure are shown in Table 1.

TABLE 1.—CHANGES IN BLOOD PRESSURE WITH NITRIC OXID

Time.	Carotid Pressure.	Pulmonary Artery Pressure.	Remarks.
	110	13.5	Before giving nitric oxid.
36 seconds	66	11.0	After beginning nitric oxid.
72 seconds	60	9.0	Inhaling nitric oxid continuously
250 seconds	56	8.0	Inhaling nitric oxid continuously.
300 seconds	32	6.0	Amount of nitric oxid increased.
480 seconds	0	0.0	Very marked pulmonary edema.

At no time throughout the course of this experiment was there an increase in pressure in the pulmonary artery. To consider a disturbance in the ratio between the two pressures as of importance in supporting Welch's theory is more or less fallacious, as drugs like nitroglycerin cause a very marked fall in the carotid pressure without affecting the pressure in the pulmonary artery. If mere disturbance of the ratio was an important factor, pulmonary edema would develop under these circumstances. In this experiment of producing acute pulmonary edema by means of nitric oxid, we were unable to detect any evidence of disproportion in the work of the two sides of the heart. The pulmonary pressure steadily fell. There were no signs of overdistention of any single cardiac chamber, or of one side of the heart. For this reason it would be impossible to apply Welch's theory to explain the development of the edema. It would appear that irritation of the bronchial or alveolar epithelium or the underlying vessels was an important factor. Cohnheim and Lichthein demonstrated that in animals in which they had produced a hydremic plethora by transfusion, irritation of the skin with iodin or exposure to the sun was sufficient to produce a local edema. We must bear in mind that in Cohnheim's experiments a predisposition to edema was present. Whether such a predisposing factor is essential in the lungs, it would be impossible to say. There is no evidence in any case that this predisposing factor is a disproportion in work of the two ventricles.

Ammonia Vapor.—The results obtained by inhalation of ammonia vapors were similar to those produced by the nitric oxid. It was neces-

sary, however, to expose the animal for a much longer period of time; the edema was less marked and of the pale type.

Carbon Monoxid.—When the gas was administered slowly the carotid pressure was very slightly lowered; the pressure in the pulmonary artery unchanged or at times showed a very slight rise. When the gas was administered more freely, a point was reached where the systemic pressure dropped suddenly to zero, with extreme slowing followed promptly by cardiac standstill. During this time the pressure in the pulmonary artery rapidly fell, standstill of both ventricles occurring at the same time. If the flow of gas was stopped, the heart gradually returned to normal. In none of our attempts, either by prolonged slow administration or the free use of the gas, were we able to produce a pulmonary edema, although, following Powkowsky's advice, young dogs were used. The experiment was repeated on rabbits; they appeared much more tolerant of the gas than dogs; prolonged free inhalation was required to bring about cardiac standstill and the lungs were free from involvement.

Hydrocyanic Acid.—Sahli referred to the frequency of pulmonary edema in dogs after poisoning with hydrocyanic acid. In Germany it is apparently a practice among veterinarians to kill incurable or suffering dogs in this way. Sahli unsuccessfully attempted to produce pulmonary edema in rabbits with the hydrocyanic acid. We used the dilute acid of the U. S. Pharmacopeia. This we administered in various ways by mouth, directly into the stomach, subcutaneously and intravenously, but were unable to produce even a moderate pulmonary edema. There was a slight fall in the carotid pressure, the pulmonary pressure remaining unchanged or showing a very gradual lowering, except in one animal in which we obtained a drop of 30 mm. Hg. in the carotid pressure with a rise of 3 mm. Hg. in the pulmonary artery, independent of any struggling, without, however, producing an edema. This single case is suggestive on account of the evidence of disproportion of work between the two sides of the heart. With stronger solutions or in certain animals this difference in pressure might reach a sufficient degree to give rise to a pulmonary edema.

Iodids.—Lugol's solution was used in these experiments; in the first series of 10 per cent., in the second series a 50 per cent., and in the third series the undiluted solution. In Series 1 the animal received intravenously 200 c.c. of the 10 per cent. solution within a period of twenty minutes. There was a sharp rise in the carotid pressure immediately after the injection was begun, this high pressure being maintained until about 180 c.c. had been injected; following this there was a rapid fall and cardiac standstill. Toward the end the heart became irregular; long

vagus strokes appeared and continued until the end. After the injection of 100 c.c. there was a gradual rise in pressure in the pulmonary artery, which was maintained during the beginning of the fall in the carotid pressure (Table 2).

TABLE 2.—CHANGES IN BLOOD PRESSURE WITH 10 PER CENT. LUGOL'S SOLUTION

Time.	Carotid Pressure.	Pulmonary Pressure.	Remarks.
	130	30	Previous to giving Lugol's sol.
30 seconds	150	32	Transfusion with 10% Lugol's sol.
270 seconds	175	40	Had received 100 c.c. Lugol's sol.
900 seconds	180	44	Had received 150 c.c. Lugol's sol.
1200 seconds	50	40	Had received 180 c.c. Lugol's sol.
1320 seconds	0	0	Very slight pulmonary edema.

During the rise in pulmonary pressure the right ventricle and right auricle dilated, the left ventricle and auricle remained normal in size throughout the experiment. The lungs showed a moderate degree of hemorrhagic edema.

In the second series the animal received 60 c.c. of a 50 per cent. Lugol's solution, in doses of 20 c.c. each, extending over a period of eleven minutes. The animal was a young dog weighing 5 kilos. During the preparation the blood pressure became very low. After the first dose of Lugol's solution there was a distinct rise in the carotid pressure, which was maintained until the animal had received 60 c.c., then the long vagus stroke appeared and the blood pressure fell rapidly. This was associated with a distinct rise in the pressure in the pulmonary artery, which was maintained until the end (Table 3).

TABLE 3.—BLOOD PRESSURE WITH 50 PER CENT. LUGOL'S SOLUTION

Time.	Carotid Pressure.	Pulmonary Pressure.	Remarks.
	36	8	Previous to giving Lugol's sol.
30 seconds	40	10	After 20 c.c. 50% Lugol's sol.
300 seconds	48	11	After 20 c.c. 50% Lugol's sol.
720 seconds	0	0	After 20 c.c. 50% Lugol's sol.

The condition of the heart was the same as in the preceding experiment. Pulmonary edema was much more marked than in the first experiment.

In the third experiment the animal received three intravenous injections of 25 c.c., each of undiluted Lugol's solution. Immediately following the first injection there was a marked rise in the carotid pressure and at the same time a gradual rise in pressure in the pulmonary artery (Table 4 and Tracing 1).

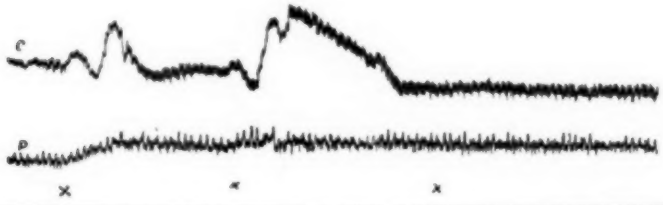
The carotid pressure quickly returned to the normal level to mount up again after the second injection; the pulmonary pressure, however, remaining high until just before death. The carotid pressure following

the third injection remained unchanged, gradually falling later. The heart was the same as in the preceding series, but the pulmonary edema was much more marked.

TABLE 4.—BLOOD PRESSURE WITH UNDILUTED LUGOL'S SOLUTION

Time.	Carotid Pressure.	Pulmonary Pressure.	Remarks.
	90	10	Previous to giving Lugol's sol.
30 seconds	110	34	After 25 c.c. Lugol's sol.
180 seconds	120	36	After 25 c.c. Lugol's sol.
300 seconds	70	36	After 25 c.c. Lugol's sol.
540 seconds	52	32	
660 seconds	0	0	Very decided lung edema.

These results are fully in accord with those of Van Zeissl. Attention is called especially to the appearance of the heart: dilatation of the right auricle and ventricle, the left auricle and ventricle normal. Van Zeissl reported the left side of the heart contracted; with this we can



Tracing 1.—Showing effect on the carotid and pulmonary arterial pressure of the intravenous injection of undiluted Lugol's solution. P, pulmonary; C, carotid; X, 25 c.c. of Lugol's solution injected.

not agree; while compared with the right side it appeared small, the size of the chambers corresponded closely to that preceding the injection. As Van Zeissl suggested that the rise in pulmonary pressure was due to constriction of the pulmonary artery, we used the various vasodilators without being able to lower the pulmonary arterial pressure. In another animal the cervical cord and vagi were cut before giving the iodid, but the rise in pulmonary pressure occurred the same as in the untreated animal. As our experience with acetic ether had shown that occasionally very large doses produced edema without a rise in pressure in the pulmonary artery, attempts were made to bring about the same results by using a very strong solution of iodin and potassium iodid. In every instance, however, a rise in the pulmonary pressure was observed. The mechanical factors favoring the development of edema were present; whether, however, they were responsible for the edema is questionable. This matter will be considered more in detail in discussing the effects of acetic ether.

Acetic Ether.—The inhalation or intravenous injection of a small amount of acetic ether invariably produces in dogs a typical pulmonary edema. The acetic ether was administered either by inhalation or intravenous injection to 17 dogs and produced an extensive hemorrhagic edema in every animal. In our early experiments doses of 2 to 3 c.c. were injected into the femoral vein; later smaller doses of 0.5 to 1 c.c. were used. Even with the smaller dose there is a distinct fall in the carotid pressure followed by a prompt partial recovery. Each succeeding dose produces a similar effect until, finally, the heart stops suddenly. With the very large doses occasionally death occurs without any rise in pressure in the pulmonary artery. More frequently, however, and invariably with the smaller doses, a very decided rise in pressure was observed. During the rise in the pulmonary arterial pressure, the right ventricle and auricle became much dilated, but we were never able to observe any dilatation of the left auricle or left ventricle. Preceding the cardiac standstill there was marked bradycardia. The left ventricle stopped first; quite regular pulsation of the right ventricle could often be observed one or two minutes after the left ventricle had ceased beating. In those animals also in which a rise in pulmonary arterial pressure did not occur, a very extensive edema was found, apparently as extensive as in those cases in which the pulmonary pressure was increased, thus showing that an increase in the pulmonary pressure is not essential for the production of edema. When the acetic ether was inhaled the same phenomena were observed, with the exception that a rise in pulmonary arterial pressure always occurred. Tables 5, 6 and 7 show the blood pressure changes and the ratio between the carotid and pulmonary pressure.

TABLE 5.—EFFECT OF LARGE DOSES OF ACETIC ETHER

Time.	Carotid Pressure.	Pulmonary Arterial Pressure.	Ratio Between Carotid and Pulm.	Remarks.
	80	14	5.7	Beginning ether.
60 seconds	44	9	4.9	After 2 c.c. acetic ether.
150 seconds	30	6	5.0	
270 seconds	14	3	4.6	After 1 c.c. acetic ether.
450 seconds	42	12	3.5	
660 seconds	56	10	5.6	
720 seconds	11	3	3.6	After 2 c.c. acetic ether.
750 seconds	0	0		Very marked edema.

In the experiment shown in Table 5 we see the pulmonary pressure never reached the height it obtained before treatment was instituted, though after the second injection of acetic ether there was a sharp rise in the pulmonary arterial pressure, at which time it approached the original level. The ratio between the blood pressure in the two ventricles

shows that, following the second injection of acetic ether, the right ventricle was doing about one-third the amount of work done by the left ventricle, while, preceding the first injection, it was only doing about one-sixth as much work as the left ventricle. Too much stress, however, should not be placed on a disturbance in the ratio as a factor in the development of pulmonary edema. Apparently an actual rise in the pulmonary pressure is essential rather than a disturbance in the relative amount of work done by the two chambers. Whether a rise in the pulmonary pressure, which follows a fall and which does not reach the original level, as in the above table, can be looked on in the same light as an actual rise in pulmonary pressure appears to the writers very doubtful.

TABLE 6.—ACETIC ETHER IN SMALL DOSES INTRAVENOUSLY

Time.	Carotid Pressure.	Pulmonary Arterial Pressure.	Ratio Between Carotid and Pulm.	Remarks.
	84	9.0	9.2	Before receiving ether.
20 seconds	64	10.5	6.3	After 1 c.c. acetic ether.
60 seconds	68	13.5	5.0	
220 seconds	80	17.5	4.6	
300 seconds	70	15.0	4.6	20 s. after 1 c.c. acet. eth.
480 seconds	36	12.0	3.0	30 s. after 1 c.c. acet. eth.
540 seconds	0	0.0	..	Very marked edema.

A very marked pulmonary edema was produced by the inhalation of acetic ether. The rise and absolute height of the pressure in the pulmonary artery was greater than we have been able to produce by any other means. Another peculiarity of this test was a decided gradual rise in the pulmonary pressure without a fall in the carotid pressure. Later, when the amount of ether was increased, a very marked fall in carotid pressure took place.

TABLE 7.—INHALATION OF ACETIC ETHER

Time.	Carotid Pressure.	Pulmonary Arterial Pressure.	Ratio Between Carotid Pressure.	Remarks.
	108	24	4.5	Before acetic ether.
120 seconds	108	32	3.5	2 min. after beginning inhalation.
240 seconds	40	32	1.2	4 min. after beginning inhalation.
360 seconds	80	40	2.0	6 min. after beginning inhalation.
480 seconds	54	44	1.2	8 min. after beginning inhalation.
600 seconds	104	48	2.1	Ether discontinued for one minute.

As we had determined that pulmonary edema could be produced with large doses of acetic ether, without an increase in the pulmonary pres-

sure, it was important to determine whether with the small doses a rise in the pulmonary pressure was essential for its development. Auscultation over the lungs revealed the presence of numerous râles following the injection of small doses, and before a rise in pressure in the pulmonary artery took place. As a further test the heart and lungs were quickly removed just at the moment a rise in the pulmonary pressure was observed, in one instance within two seconds. Under these circumstances marked pulmonary edema had already developed. This experiment was repeated several times with always the same result. We must, therefore, conclude that the rise in pressure in the pulmonary artery really took place after the edema had appeared.

In endeavoring to explain the increase in the pulmonary arterial pressure, without evidence of stasis in the left heart, the possibility that the edema might cause the rise in pressure was considered. It is con-

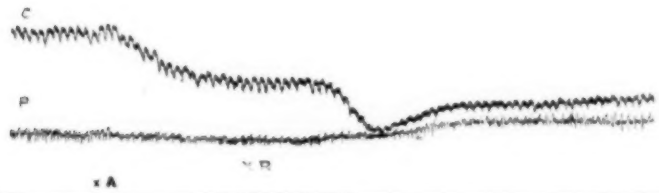
Tracing 2.—Effect on the blood pressure of small doses of acetic ether injected intravenously. P, pulmonary artery; C, carotid; X, 1 c.c. of acetic ether injected into the femoral vein. Very marked pulmonary edema.

ceivable that the pressure exerted on the arterioles of the pulmonary artery by the distended alveoli might increase the resistance sufficiently to cause such a rise in pressure. The effect on the blood pressure of overdistention of the lung with air was first tested. We were unable, however, even after prolonged distention, to produce a rise in the pulmonary blood pressure. An attempt was then made to distend the alveoli by allowing water to flow slowly down the trachea. An 8-kilo dog received in this way 250 c.c. of water in a period of 10 minutes. After the instillation of 100 c.c. a gradual rise in the carotid pressure was noted, which slowly increased until 175 c.c. had been given, when a gradual fall set in, which continued as long as the instillation of water was kept up. With the beginning of the rise in the carotid pressure, there was a gradual increase in pressure in the pulmonary artery, which reached its maximum much later than the maximum rise in the carotid. Following this there was a slight fall in pressure not commensurate, however, with the fall in the carotid. These blood-pressure changes are shown in Table 8. The lungs of this animal had the same appearance as those with pul-

monary edema. Abundance of bloody froth could be expressed from the large bronchi, and red blood corpuscles and granular material were found in the alveoli on microscopic examination. Apparently the instillation of water produced a pulmonary edema, and, therefore, the rise in pressure in the pulmonary artery was not necessarily due directly to the instillation of the water.

TABLE 8.—EFFECT ON CAROTID AND PULMONARY PRESSURE OF INSTILLATION OF WATER INTO THE TRACHEA

Time.	Carotid Pressure.	Pulmonary Arterial Pressure.	Remarks.
	130	19.0	Before instillation began.
200 seconds	156	22.0	After 125 c.c. of water.
240 seconds	170	23.5	After 175 c.c. of water.
330 seconds	90	26.0	After 200 c.c. of water.
450 seconds	68	21.0	After 220 c.c. of water.
600 seconds	10	17.0	After 250 c.c. of water.

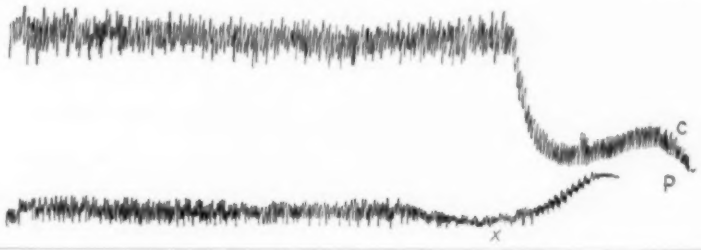


Tracing 3.—Showing the effect of acetic ether after section of the cord in the mid-cervical region. A, cord cut; b, 1 c.c. acetic ether intravenously.

From a study of the edema produced by iodids, we must conclude that with this agent, at least, the edema is not the cause of the rise in pressure in the pulmonary artery, as Van Zeissl determined that animals killed a few seconds after the increase in pulmonary pressure began did not show edema, but that prolonged increase in pressure was essential for its development. The rise in pressure in the pulmonary artery after acetic ether could not be prevented or modified by large doses of nitroglycerin. Combined section of the cord in the mid-cervical region and of the vagi also failed to prevent or modify it. The effect of section of the cord is shown in Tracing 3. It would, therefore, appear that the rise in pressure in the pulmonary artery is not of nerve origin. A close study of Tracing 4 would certainly give the impression that stasis from the left heart was a factor, as we note in the tracing that the increase in pressure in the pulmonary artery begins during the period of sudden drop in the carotid pressure, exactly what could be expected if stasis were the cause. If we could accept Löwit's explanation that direct transmission of pressure from the left auricle through the pulmonary veins to the pulmonary artery does not necessarily occur, and that increased

pressure in the pulmonary artery is not necessarily transmitted to the pulmonary veins, stasis could still explain this phenomenon.

In seeking for an explanation of the rise in the pulmonary arterial pressure without corresponding increase in pressure in the left auricle, it was suggested that capillary thrombosis might be responsible. We can readily see that a plugging of the terminal branches of the pulmonary artery would be followed by the above pressure changes. Silbermann[17] has shown that capillary thrombosis may be readily induced by various toxic agents, including carbon monoxid and ether, and that the capillaries of the lungs, on account of their exceedingly small caliber and low blood pressure, are especially prone to thrombosis. To demonstrate that such thrombosis was antemortem, Silbermann injected 400 to 500 c.c. of a saturated watery solution of indigo-carmin into a vein of the living animal. The areas of tissue in which the capillaries were plugged



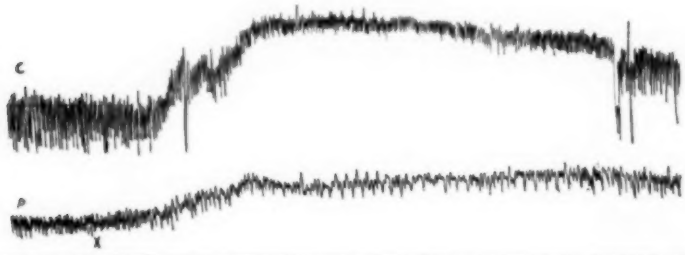
Tracing 4.—Showing the simultaneous changes taking place in the carotid and pulmonary pressure after acetic ether. C, carotid; P, pulmonary artery; X, 0.5 c.c. acetic ether intravenously.

would not be colored, while tissues with patulous vessels would take the stain. We resorted to this test in animals that had previously received iodid or acetic ether in sufficient amounts to cause pulmonary edema, but were unable to demonstrate the presence of capillary thrombosis. Microscopic examination of sections of the lung also gave negative results.

Adrenalin Chlorid.—On account of the occasional recurrence of pulmonary edema in rabbits after the intravenous injection of adrenalin chlorid, an attempt was made to study the blood-pressure changes during the development of such an edema. With cannulas in the carotid and pulmonary arteries efforts were made to produce a pulmonary edema by intravenous injection of 0.5 to 2 c.c. of a 1:1,000 solution of adrenalin

17. Silbermann, O.: Ueber das Austreten multiples intravitales Blutgerinnungen nach acuter Intoxication durch Chlorsäure Salze-Arsen, Phosphor und einige andre Blutgifte. Virchow's Arch. f. path. Anat., 1889, cxvii, 288.

chlorid. Although the experiment was repeated on a considerable number of rabbits, we were never able to obtain one in which a pulmonary edema could be produced by this measure. The experiment was then modified by cutting off part of the circulation. The descending portion of the thoracic aorta was ligated, beyond where the large trunks are given off to the head and upper extremities. This ligation was followed by a very marked rise in the carotid pressure; the pressure in the pulmonary artery, however, was not affected; nor did pulmonary edema develop. The animal then received 0.5 c.c. of a solution of adrenalin chlorid, which caused a still further rise in the carotid pressure in the pulmonary artery, and the development of a marked pulmonary edema. This same experiment was repeated on dogs with similar results. These pressure changes are shown in Table 9 and also in Tracing 5.



Tracing 5.—Effect of adrenalin after ligation of the thoracic aorta. C, carotid; P, pulmonary artery; X, 1 c.c. adrenalin chlorid 1-1,000.

TABLE 9.—EFFECT OF ADRENALIN AFTER LIGATION OF THE THORACIC AORTA

Time.	Carotid Pressure.	Pulmonary Arterial Pressure.	Remarks.
	106	9	Before ligation of aorta.
	146	7	After ligation of aorta.
30 seconds	210	19	After 1 c.c. adrenalin chlorid 1:1000.
120 seconds	204	18	Animal killed; pulmonary edema.

The development of pulmonary edema in these animals can best be explained by the vasoconstrictor action of the adrenalin raising the pressure in the systemic circulation to such a degree that the left ventricle is unable to empty itself completely. Stasis in the left auricle, pulmonary vein and pulmonary artery then follows with a consequent rise in pressure in the pulmonary artery and the development of edema. This is quite in accord with the theory advanced by Meltzer to explain the pulmonary edema following the use of adrenalin. By slow transfusion with a solution of adrenalin chlorid, 1:1,000,000, we were able to maintain a very high carotid pressure for twenty minutes, the pulmonary pressure

also showing a decided rise in case the thoracic artery had been previously constricted. Edema under these circumstances is of especial interest, as its development is associated with high pressure in the systemic circulation. One of the strongest arguments against the clinical application of Welch's theory is that it did not account for the high tension pulse often seen during an attack. In nephritis with extremely high blood pressure, the failure of the left ventricle to empty itself completely, with resulting stasis, increase in pressure in the pulmonary artery, and development of acute pulmonary edema, with high tension pulse, may occur exactly as it does in the rabbit after the use of adrenalin. It is well understood that high systolic pressure may be associated with small systolic output provided the pulse pressure, i. e., the difference between the systolic and diastolic pressure, is reduced. A high-tension pulse does not necessarily imply normal systolic output.

Tracing 6.—Effect of bleeding, after artificial mitral stenosis. X′, 15 c.c. of blood withdrawn from the jugular. 15 c.c. withdrawn at X″ X‴ X⁗; C, carotid; P, pulmonary.

Artificial Mitral Stenosis.—The effect on the pulmonary pressure and the development of pulmonary edema was studied in dogs in which an artificial stenosis had been produced. With a little practice a ligature may be passed through the auriculoventricular groove in such a manner that on tightening it any degree of mitral stenosis may be produced. The first effect of narrowing the orifice is a fall in the carotid pressure. This occurs only after a considerable degree of constriction. In one animal the orifice was reduced one-half in size with only slight effect on the carotid pressure. When the constriction is carried still further, a rise in pressure in the pulmonary artery takes place. This rise may be slight or very marked, depending on the degree of obstruction induced. Table 10 shows the changes of blood pressure after constriction of the orifice from 8 to 3 mm. All of these animals when a satisfactory constriction of the orifice was obtained developed a decided pulmonary edema of the hyperemic type. After the constriction had reached a moderate degree, dilatation of the left auricle occurred followed by dilatation of the right auricle and right ventricle. The development of edema under these circumstances is best explained by Welch's theory.

TABLE 10.—PULMONARY AND CAROTID PRESSURE FOLLOWING MITRAL STENOSIS

Time.	Carotid Pressure.	Pulmonary Arterial Pressure.	Remarks.
	100	9	Before production of stenosis.
60 seconds	50	9	Slight constriction mitral orifice.
300 seconds	84	14	Orifice constricted from 8 to 3 mm.
420 seconds	80	18	Showing increase in pulmonary pressure although no change in constriction since previous reading.

EXPERIMENTAL THERAPEUTIC AGENTS

In applying therapeutic agents to the treatment of experimental edema, it can readily be seen that no single remedy would be indicated in all instances. While the pulmonary arterial pressure was increased in most forms of experimental edema, the systemic blood pressure varied, low in some instances, high, however, in that type produced by adrenalin. Assuming that mechanical factors are important, a drug or method of treatment, in order to be considered beneficial, should tend to equalize the work of the cardiac chambers. The only form of experimental edema that yields readily to treatment is that produced by muscarin. Atropin has here a physiologic antagonistic action, and under its use the left ventricle assumes its normal working power, the blood pressure becomes equalized and the edema gradually subsides. Atropin, however, in pulmonary edema from other causes was without beneficial effect. When used in the edema produced by acetic ether or iodids the pressure in both carotid and pulmonary artery was increased, the developing edema was not checked nor was the life of the animal prolonged.

Nitroglycerin was also tried in the edema produced by acetic ether and iodids with the idea that perhaps the rise in pressure in the pulmonary artery was in part due to a vasoconstrictor action. As previously mentioned, however, large doses of nitroglycerin under these circumstances did not reduce the pulmonary arterial pressure. In the edema induced by adrenalin with high systemic pressure, the nitroglycerin was ineffectual on account of its action being interferred with by the more powerful adrenalin. This does not mean, however, that in pulmonary edema of this type in man nitroglycerin might not be beneficial, as the high tension in the systemic circulation may be due to other agents than adrenalin, which yield, slightly at least, to the vasodilators.

Barium chlorid, on account of its constriction of the pulmonary artery, due to its action directly on the unstriated muscle, was tried both for the prevention and alleviation of experimental pulmonary edema. As there is hyperemia of the lung with the edema, and the theory has been advanced that pulmonary edema is due to vasomotor paresis of the

pulmonary artery, it was thought that barium chlorid might exert a desirable influence. The results, however, were entirely negative either as regards preventing the edema or modifying its course. Changes in pressure in the carotid and pulmonary artery occurred as in the untreated animals.

Digitalis was also tried, both in preventing and alleviating developed edema. The only form of edema in which it appeared to have any beneficial action was that due to artificial mitral stenosis. Here in conjunction with venesection it contributed to the equalization of the circulation.

The effect of venesection was noted in animals with acute pulmonary edema from the various causes. The results on the whole were quite disappointing. Before any effect could be seen on the pressure in the pulmonary artery, it was necessary to withdraw a sufficient amount of blood to lower the general blood pressure materially. Rapid withdrawal of 10 to 20 c.c. of blood from the jugular vein of a 12-kilo dog would lower the pressure in the pulmonary artery momentarily, but it would promptly return to the previous level (see Curve 5). The withdrawal of 100 c.c. within two minutes in an 8-kilo dog would cause a permanent fall in both carotid and pulmonary artery, which, however, could not be considered as beneficial. When digitalis was given in conjunction with moderate bleeding, in the edema due to mitral stenosis, the pulmonary pressure could be lowered slightly and the carotid pressure raised to its previous level. It was not determined whether this increase in pressure in the systemic circulation was due to increased systolic output or to general vasomotor constrictions; however, as there was a slight fall in pressure in the pulmonary artery apparently the systolic output of the left ventricle was somewhat increased. With the adrenalin edema better results were obtained by bleeding from an artery than from a vein.

Although our therapeutic results in the treatment of experimental edema were so unsatisfactory, a knowledge of the factors at work in producing an edema should be of assistance in its intelligent treatment. We must remember that many attacks of acute pulmonary edema in man subside without treatment and, for this reason, clinical experience in the value of therapeutic agents must be accepted with considerable reserve. Considering marked disturbance of the circulation as the chief underlying cause of the trouble, intelligent rather than empirical treatment should be instituted. To give adrenalin, digitalis or caffein in a case of edema associated with high arterial tension might hasten a fatal termination. Atropin under these conditions, on account of its raising the blood pressure by quickening the heart action, would not be indicated. In this type of edema efforts should be directed toward lowering the

arterial tension, by the vasodilators or counter-irritation to the surface of the body or by bleeding with the type of edema associated with low-tension pulse, this form of treatment might be injurious. Here digitalis and caffein would be indicated. It is interesting to note the frequency with which atropin is recommended in the treatment of acute pulmonary edema. The foundation of this treatment is apparently its beneficial results in the edema due to poisoning with toadstools and pilocarpin. The pulmonary edema developing in nephritics after the use of pilocarpin is often due in reality to the drug, as it produces edema in the same manner as muscarin, and atropin is the physiologic antidote. The second reason for its general use is based on its power to lessen glandular secretion. It is unnecessary to state that in acute pulmonary edema we are not dealing with a glandular secretion, but a transudation. The use of adrenalin is to be discouraged as being, under certain conditions, very dangerous and probably always valueless. Oxygen inhalations are harmless and give some temporary relief and may assist in tiding the patient over. Morphin, by allaying the patient's fears, is decidedly beneficial in its effects and could be safely used in small doses in any type of acute pulmonary edema. Venesection is another measure which is probably safe if practiced on individuals not already decidedly anemic. Its real value, however, can only be determined by extensive clinical observations. Unfortunately for the science of medicine, no one physician is able to see a sufficient number of cases of acute pulmonary edema during his lifetime to make a careful comparative study of the value of the various forms of treatment.

CONCLUSIONS

1. When pulmonary edema develops after exposure to nitric oxid or ammonia, there is no evidence that mechanical factors play a rôle; i. e., we are unable to detect any evidence of disproportion between the working power of the two sides of the heart.

2. The acute pulmonary edema following inhalation or intravenous injection of acetic ether is usually associated with evidence of disproportion in the working power of the two sides of the heart, as there is a fall in the systemic and a corresponding rise in pressure in the pulmonary artery. When large doses of acetic ether are injected intravenously, pulmonary edema may occur without evidence of disproportion in the working power of the two sides of the heart, thus showing that such changes are not essential for its appearance. It would appear, therefore, that mechanical factors are not responsible for the edema.

3. In the acute pulmonary edema produced by iodids, there is in the beginning a marked rise in pressure in both the systemic and pulmo-

nary circulation; later the systemic blood pressure falls, but the pressure in the pulmonary artery remains high. This disproportion in the working power of the two ventricles was present in every instance; it would, therefore, appear from our experiments that the edema might be explained by mechanical agents, although not necessarily so.

4. The intravenous injection of adrenalin chlorid, when preceded by ligation of the thoracic aorta, causes pulmonary edema. Apparently as a result of the great increase in the systemic blood pressure after such a procedure, the left ventricle is unable to empty itself completely; stasis and rise in pressure in the pulmonary artery follows. This is perhaps the mechanism of acute pulmonary edema in nephritics with hypertension.

5. In the mechanical edemas, therapeutic measures to be of value should tend to equalize the work of the cardiac chambers. This may mean the use of vasodilators in some instances, in others the use of drugs that stimulate the heart activity.

100 State Street.

A COMPARATIVE STUDY OF SERUM DIAGNOSIS IN SYPHILIS *

HOMER F. SWIFT, M.D.
NEW YORK

Although only three years have elapsed since the Wassermann-Neisser-Bruck reaction for the diagnosis of syphilis was described, it has become in this time a well-established diagnostic method and it, or its modifications, are now in use in all large medical centers. During this period, which must be considered as a stage of experimentation and testing, a number of modifications of the original method, and also several practically new methods for serum diagnosis have been devised. Several of these have been subjected to critical examination by various investigators, and although from the mass of evidence the original method, with a slight modification, appears to be the most satisfactory, it has seemed to me advisable to carry out a comparative, critical study of the more important modifications. The methods selected for study are the following:

I. Wassermann's original method.

II. Noguchi's precipitation method for spinal fluids, with a discussion of the precipitation reactions of Porges, Fornet, Klausner and Noguchi for blood serum.

III. Bauer's simplification of the Wassermann reaction, with a discussion of Tschernogubow's modification.

IV. Noguchi's complement deviation method.

I. THE WASSERMANN METHOD

In his adaptation of the Bordet-Gengou phenomenon of complement deviation, Wassermann used as a hemolytic system: (a) 1 c.c. of a 5 per cent. suspension of washed red blood cells of the sheep; (b) two units[1] of hemolytic amboceptor made by immunizing rabbits to sheep's red

*From the Department of Pathology, The Carnegie Laboratory, The University and Bellevue Hospital Medical College, aided by a grant from the Committee on Scientific Research of the American Medical Association. Read before the Association of American Physicians, Washington, May 12, 1909, and by title before Section on Physiology and Pathology of the American Medical Association, Atlantic City, June, 1909.

1. The hemolytic unit is the amount of inactivated hemolytic serum that will completely hemolyze 1 c.c. of a 5 per cent. suspension of sheep's red blood cells in the presence of 0.1 c.c. of fresh guinea-pig serum as complement.

blood cells; and (c) as complement 0.1 c.c. fresh guinea-pig serum. For syphilitic antibody 0.2 c.c. of serum from suspected patients was selected as the maximum quantity; and for antigen a watery extract of a liver of congenital syphilis known to be rich in *Spirochæta pallida*.

At this time Wassermann considered his antigen to be an extract of the specific organism and the fixation of complement to be therefore a true antigen-antibody reaction. The subsequent work on the nature of the antigen has, however, destroyed this view. Marie and Levaditi,[2] in applying the reaction to the spinal fluid from tabes and general paralysis, found that extracts of livers from non-syphilitic fetuses gave a weak reaction, and such extracts when used in large quantities acted satisfactorily as antigens. Weil,[3] using extracts of tumors, obtained positive reactions with syphilitic sera, and from such results he attacked the specificity of the method. Such results clearly proved that the so-called antigen was not the *Spirochæta pallida* or its products, and numerous workers took up the study of the nature of this substance. Under Wassermann's[4] direction, alcoholic extracts of syphilitic livers were made and found to contain the active substance. Similar experiments[5] were repeated with the normal organs of man and the lower animals and all such extracts were found to be potent antigens. As extraction by alcohol indicated the substance to be lipoid in nature, different members of the lipoid group, in the pure state, were tested. Among these may be mentioned lecithin, cholesterin, the sodium salts of the bile acids, sodium oleate and oleic acid. Combinations of these in definite proportions have been suggested for us as antigen, but so far the total extracts of organs seem to act the best, and of these, extracts of syphilitic organs can be used in the smallest quantity.

To be satisfactory an antigen should possess the following qualities: (1) It should not prevent hemolysis when mixed with the hemolytic system; (2) it should give a positive reaction in a large proportion of syphilitic cases and should not react with non-syphilitic sera; (3) it should retain its antigenic qualities for some time so that comparative tests may be made.

The watery extracts are prone to undergo sudden changes, while the alcoholic extracts keep well at room temperature. Each antigen must be tested as to the first two qualities before it is finally adopted as a reagent. It would be a great advantage if some rule could be formulated for the

2. Marie, A., and Levaditi, C.: Ann. de l'Inst. Pasteur, 1907, xxi, 138.
3. Weil, E.: Wien. klin. Wchnschr., 1907, xx, 527.
4. Wassermann, A.: Berl. klin. Wchnschr., 1907, xliv, 1599.
5. Porges, O., and Meier, G.: Berl. klin. Wchnschr., 1908, xlv, 731.

making of antigen, but as yet no definite antigen has been generally adopted. In many places alcoholic extracts of animal organs are used and Wassermann[6] lately admits that such antigens may be employed provided they have been previously compared with a known antigen. He, however, prefers the watery extract for doubtful or weak sera.

In the first hundred tests by the Wassermann method in this report (see Tables 3 to 9) the antigen was a 0.1 per cent. emulsion of lecithin furnished by Dr. Noguchi of the Rockefeller Institute; in the later cases an alcoholic extract of dog's liver was used and found to work in a satisfactory manner. This has been lately compared in about one hundred tests with an alcoholic extract of syphilitic liver and the latter has been found to give somewhat more marked reactions with weak sera.

On account of the small amount of blood obtained by puncture of the ear, hardly sufficient for the numerous controls necessary, I have found it advisable to reduce the quantities of serum and complement by one-half that recommended in the original method, that is, to use 0.1 c.c. of the patient's serum and 0.05 c.c. of guinea-pig's serum to each tube. The other factors were reduced in the same proportion. Some investigators have used the drop method to economize serum, but I thought it better to reduce all the reagents in a definite proportion.

II. PRECIPITATION METHODS

The complicated nature of the Wassermann reaction has led to many attempts to simplify the serum diagnosis of syphilis. Various precipitation methods have been devised, but found not to be specific. Among them may be mentioned the Porges[7] reaction with lecithin, the Fornet[8] reaction, by mixing serum from florid syphilis with that from parasyphilis, and the Klausner[9] reaction, which demonstrated an increase in globulin by mixing suspected sera with distilled water. Noguchi[10] demonstrated an increase in globulins by precipitating these bodies with a one-half saturated solution of ammonium sulphate, centrifuging, pouring off the supernatant fluid, redissolving them in normal salt solution, and adding 10 per cent. butyric acid. A flocculent precipitate in two hours was considered evidence of a decided increase in the globulin fraction. While this increase of globulin is often found in syphilis, it is not pathognomonic, for it is present in many other infectious diseases, and earlier

6. Wassermann, A.: Deutsch. med. Wchnschr., 1909, xxxv, 418.
7. Porges, O.: Wien. klin. Wchnschr., 1908, xxi, 206.
8. Fornet and Schereschewsky: München. med. Wchnschr., 1907, liv, 1471.
9. Klausner, E.: Wien. klin. Wchnschr., 1908, xxi, 214.
10. Noguchi, H.: Jour. Exper. Med., 1909, xi, 84.

experimental work has shown that the formation of immune bodies, both to bacteria and other organic substances, frequently is accompanied by an increase in globulin. Noguchi himself has called attention to the fact that the increase is found in many other conditions.

Noguchi[10] also devised a precipitation method for detecting an increase of the protein of the spinal fluid in parasyphilitic diseases. By boiling 0.1 c.c. of the fluid with 0.5 c.c of a 10 per cent. butyric acid solution and adding 0.1 c.c. of normal sodium hydroxid solution, and again boiling, a granular precipitate is obtained. This reaction he at first considered diagnostic, but later found it in other forms of meningitis. Gay and Fitzgerald[11] confirmed Noguchi's findings in tabes and general paralysis, but obtained the same reaction in meningitis, and some psychopathic conditions. In applying this test to spinal fluids, I obtained the reaction in three cases of tuberculous meningitis, two of gastro-enteritis with symptoms of meningeal irritation, one of alcoholic cerebral edema, and one of pneumonia. The spinal fluid from a case of congenital syphilis and that from an autopsy of a man with visceral syphilis also gave the granular precipitate. The non-specificity of the reaction prevents its use as a diagnostic measure, although it may be applied in cases of known syphilis to determine if the syphilitic process is active in the central nervous system.

III. BAUER'S MODIFICATION OF WASSERMANN'S METHOD

The failure of the various precipitation reactions as reliable diagnostic measures forces us to fall back on the complement deviation method. Various attempts have been made to simplify the original process. It was noted that frequently the tubes under trial showed hemolysis before the control tube without serum, and such observations led to the discovery that many sera possessed the power of hemolyzing sheep cells without the addition of the hemolytic serum from an immunized rabbit. Taking advantage of this, Bauer[12] omitted the addition of foreign hemolytic serum. In other respects his procedure is practically that of the original method. He mixes the suspected serum with complement and antigen, incubates to bind complement, and then adds only sheep cells and again incubates. As a control he uses the serum from a non-syphilitic person. His protocol would read thus:

11. Gay, F. P., and Fitzgerald, J. G.: Boston Med. and Surg. Jour., 1909, clx, 157.

12. Bauer, J.: Deutsch. med. Wchnschr., 1908, xxxiv, 698.

PROTOCOL I.—BAUER METHOD.

	Test for Diagnosis.	Control Set with Normal Serum.
Control tubes without Antigen.	Tube 2. a. Patient's serum containing hemolysin (and syphilitic antibody?)	Tube 4. a. Normal serum containing hemolysin.
	b. Complement.	b. Complement.
Determinative tubes with Antigen.	Tube 1. a. Patient's serum containing hemolysin (and syphilitic antibody?)	Tube 3. a. Normal serum containing hemolysin.
	b. Complement.	b. Complement.
	c. Antigen.	c. Antigen.
	Incubation at 37 C. for 1 hour. Washed sheep's red blood cells. Incubation at 37 C. for 2 hours.	Then in ice-box over night.

If hemolysis is inhibited in Tube 1 the reaction is positive. This method has been adopted in a few clinics in Germany. Bering[13] reports that the method gives as good results as the original Wassermann method, and prefers it because it is simpler and requires less of the patient's serum. Hinrichs[14] finds it more satisfactory and reports the results as given in Table 1.

TABLE 1.—HINRICH'S COMPARISON OF BAUER AND WASSERMANN METHOD

Type of Syphilis.	Bauer Method. % Positive.	Wassermann Method. % Positive.
Untreated	100	100
Fairly well treated	70	40
History of over four years, little treated.	87	65
History of over four years, well treated..	66	50

Meirowsky[15] did not find it so reliable and obtained a higher per cent. of positive results in the Wassermann reaction. Noguchi reports having tried the method in over a hundred cases and says that it is unreliable because of the inconstant content of anti-sheep amboceptor.

I have compared this method with those of Wassermann and Noguchi in sixty-five cases of syphilis and thirty-two non-syphilitic individuals. The results with the syphilitic sera are given in Table 2. The control sera, all negative with the Wassermann method, showed complete hemolysis in eleven cases, partial in thirteen, slight in three and none in five. The control tubes with the syphilitic sera showed complete hemolysis in twenty-six cases and insufficient or no hemolysis in thirty-nine. The whole number shows 37 sera, or 38 per cent., with sufficient anti-sheep amboceptor to perform the test, and 60 sera, or 62 per cent., with an insufficient amount. Of the cases of syphilis, 65 per cent. reacted posi-

13. Bering, F.: München. med. Wchnschr., 1908, lv, 2476.
14. Hinrichs. Med. Klinik., 1908, iv, 1349.
15. Meirowsky, E.: Berl. klin. Wchnschr., 1909, xlvi, 152.

TABLE 2.—COMPARISON OF WASSERMANN, NOGUCHI AND BAUER REACTIONS *

No.	Wassermann.	Noguchi.	Amount of Hemolysis in Test Tube.	Amount of Hemolysis in Control Tube.	Amount of Hemolysin.	Result.
			PRIMARY SYPHILIS.			
190	++	++	None	Nearly Complete.	Sufficient.	++
245	++	++	None.	Complete.	Sufficient.	++
492	+	+	None.	Complete.	Sufficient.	++
			SECONDARY SYPHILIS.			
192	++	+—	None.	Partial.	Insufficient.	+?
196	++	++	None.	None.	Insufficient.	?
218	++	++	None.	Partial.	Insufficient.	+?
236	++	++	None.	Complete.	Sufficient.	++
241	—	—	None.	Complete.	Sufficient.	++
257	++	++	None.	Complete.	Sufficient.	++
499	+	+	None.	Complete.	Sufficient.	++
			TERTIARY SYPHILIS.			
171	—	+	Slight.	Complete.	Sufficient.	+
173	++	++	None.	Nearly Complete.	Sufficient.	+
204	++	+	None.	None.	Insufficient.	?
220	++	+	None.	Complete.	Sufficient.	++
221	++	+	None.	Slight.	Insufficient.	+?
235	++	++	None.	Slight.	Insufficient.	+?
256	++	++	None.	Partial.	Insufficient.	+?
537	++	++	None.	Complete.	Sufficient.	++
			LATENT SYPHILIS.			
184	+	+—	Partial.	Partial.	Insufficient.	?
213	+	+	None.	Complete.	Sufficient.	++
222	+—	—	Partial.	Partial.	Insufficient.	?
223	—	—	None.	None.	Insufficient.	?
224	—	+—	Partial.	Partial.	Insufficient.	?
243	—	—	None.	None.	Insufficient.	?
244	—	—	None.	None.	Insufficient.	?
246	+	++	Slight.	Partial.	Insufficient.	?
249	—	+	Partial.	Partial.	Insufficient.	?
254	—	+	None.	None.	Insufficient.	?
489	+—	+	Slight.	Complete.	Sufficient.	+
494	+—	+	None.	Complete.	Sufficient.	++
514	—	—	Partial.	Partial.	Insufficient.	?
518	+—	+—	Slight.	Slight.	Insufficient.	?
534	—	—	Complete.	Complete.	Sufficient.	—
536	++	++	None.	None.	Insufficient.	?
			VISCERAL SYPHILIS.			
178	+—	+—	Partial.	Partial.	Insufficient.	?
181	++	++	None.	Nearly Complete.	Sufficient.	++
182	—	—	None.	None.	Insufficient.	?
187	+	+—	None.	Partial.	Insufficient.	+?
188	+	—	Slight.	Slight.	Insufficient.	?
193	—	—	Slight.	Slight.	Insufficient.	?
195	+	+—	Slight.	Complete.	Sufficient.	+
202	—	—	Complete.	Complete.	Sufficient.	—
211	—	—	Partial.	Partial.	Insufficient.	?
215	—	—	Complete.	Complete.	Sufficient.	—
219	++	++	None.	None.	Insufficient.	?
226	+—	+	None.	Slight.	Insufficient.	+?
227	++	++	None.	Slight.	Insufficient.	+?
229	—	—	None.	None.	Insufficient.	?
247	—	+	Complete.	Complete.	Sufficient.	—
503	—	—	Slight.	Complete.	Sufficient.	+
504	—	—	Partial.	Complete.	Sufficient.	+—
508	+—	+	Slight.	Complete.	Sufficient.	+
510	+—	+	Slight.	Complete.	Sufficient.	+
			CONGENITAL SYPHILIS.			
225	++	+	None.	Slight.	Insufficient.	+?
237	++	++	None.	Slight.	Insufficient.	+?
			TABES.			
183	—	—	None.	Slight.	Insufficient.	+?
186	+	+	None.	Partial.	Insufficient.	+?
189	—	—	Complete.	Complete.	Sufficient.	—
210	+	+	None.	Slight.	Insufficient.	+?
212	—	—	Partial.	Partial.	Insufficient.	?
250	+—	++	Partial.	Partial.	Insufficient.	?
509	+—	+	None.	None.	Insufficient.	?
517	++	++	None.	Complete.	Sufficient.	++
532	—	—	Complete.	Complete.	Sufficient.	—
535	++	++	None.	None.	Insufficient.	?

* ++=Complete Inhibition.
+=Marked Inhibition.
+—=Slight Inhibition.
—=Complete Hemolysis.

tively with the Wassermann and 67 per cent. with the Noguchi method. The Bauer method gave 33 per cent. positive, 20 per cent. doubtful-positive, 9 per cent. negative and 38 per cent. in which a diagnosis could not be made. Five spinal fluids were similarly tested and none was found to contain anti-sheep amboceptor. Bauer in his original communication says that the blood of suckling infants can not be used and recommends that a little serum from a normal adult be added to that of infants. It would seem better to add a known quantity of foreign hemolytic serum so that the results could be more accurately measured.

The cause of the variation in the amount of anti-sheep amboceptor has not been explained. The thought naturally occurs that perhaps the eating of mutton excites the formation of this body and that the variations in the results from different cities may be due to the fact that this meat is used more in some places than others. Some ground for this supposition is afforded by the work of Rosenau and Anderson[16] on hypersusceptibility and immunity. They have shown that guinea-pigs may be sensitized to horse and cattle serum by feeding them horse-meat or beef, uncooked. We have no evidence, however, that the results of those experiments may be applied to man.

The fact that some samples of sera are rich in anti-sheep amboceptor explains also the negative Wassermann reactions in certain cases of evident syphilis. Morgenroth and Sachs[17] have shown that with a fixed quantity of cells, complete hemolysis will take place by varying the amount of complement and amboceptor inversely to one another. They found that with 1 c.c. of a 5 per cent. suspension of sheep's red blood cells and 0.1 c.c. of guinea-pig serum as complement, that 0.05 c.c. of rabbit's serum as amboceptor produced complete hemolysis; if 0.2 c.c. or 0.4 c.c. of the same rabbit's serum was used only 0.01 c.c or one-tenth the amount of complement was required. Other experiments showed that a fourfold increase of amboceptor caused such a change that only one-twentieth the amount of complement was needed. From this it can be readily seen that if a large hemolytic amboceptor content were present, with a small syphilitic antibody content, so that not quite all the complement was absorbed, the reaction might be negative. Noguchi[18] reports finding as high as twenty units of anti-sheep amboceptor in some samples of human serum. He also found that four units of amboceptor prevents the detection of one unit of syphilitic antibody. On account of

16. Rosenau, M. J., and Anderson, J. F.: Bull. No. 36, Hyg. Lab. U. S. P. H. and M.-H. S., Washington, 61.

17. Morgenroth, J., and Sachs, H.: Berl. klin. Wchnschr., 1902, xxxix, 817.

18. Noguchi, H.: Jour. Exper. Med., 1909, xi, 392.

these observations, if a specimen of blood under examination produces rapid hemolysis, it is well to determine the amount of antibody present. At times this will be the exact amount necessary for Bauer's modification. Case 241 under secondary syphilis (Table 3) shows this very well. In this patient the Wassermann was negative, but the Bauer positive. This serum was from a man who had become infected four months previously, had ten weeks' treatment, and presented only lesions of the soft palate. At other times the hemolytic content may be so high that the dilution required to obtain only two units of amboceptor would completely prevent the detection of a small amount of syphilitic antibody. Such a case is that of a woman who eight years ago was infected with syphilis, at which time she had a short course of treatment. She then disappeared from observation until eight months ago, when she returned to the hospital with tertiary lesions of the skin. Treatment caused these to disappear, but two months ago she began to have shooting pains in the legs and vesical symptoms. Examination revealed the Argyll-Robertson pupil, Romberg's sign, and some incoordination in the movement of the legs. The case is undoubtedly one of beginning tabes with syphilis as an etiologic factor. Treatment had been inefficient, but the serum reaction was negative with both the Wassermann and Bauer tests, but positive by Noguchi's method. Investigation showed that the amount of serum used contained five units of anti-sheep amboceptor, enough to mask the weak syphilitic antibody that would be expected. I have frequently noted that the tubes in cases of known syphilis which give a negative Wassermann reaction are the first to hemolyze, and am sure that this explains a number of negative reactions.

Meirowsky[18] says that he makes it a rule to repeat the reaction, substituting the Bauer technic for the original method, when the serum from a case strongly suspicious of syphilis fails to give the reaction. As a routine it might be well to introduce a control tube with one-half the amount of serum usually employed in the Wassermann test; if this, with 0.1 c.c. of complement, should produce complete hemolysis of the usual number of cells, it would give a clue to the cause of negative findings with certain sera, and would justify repeating the reaction with Bauer's modification.

Tschernogubow[19] described a method whereby the complement and cells present in human blood were utilized in a complemental deviation test. He diluted 0.4 c.c. of blood to 4 c.c. with normal salt solution and used 1 c.c. in each of four tubes. His source for antihuman amboceptor is not stated. Protocol 2 gives his method.

19. Tschernogubow, N.: Berl. klin. Wchnschr., 1908, xlv, 2107.

PROTOCOL II.—TSCHERNOGUBOW METHOD.

Control Without Antigen or Hemolytic Amboceptor.	Control Without Antigen.
Tube 2.	Tube 1.
a. Blood dilution containing complement and cells.	a. Blood dilution containing complement and cells.
Tube 3.	Tube 4.
Determinative Tube.	Control Without Hemolytic Amboceptor.
a. Blood dilution containing complement and cells.	a. Blood dilution containing complement and cells.
b. Antigen.	b. Antigen.

Incubation at 37 C. for 1 hour.
Add hemolytic amboceptor to 1 and 3.
Incubation at 37 C. for 2 hours.

Tube 1 shows hemolysis; Tube 2 shows no hemolysis; Tube 3 (test) will show no hemolysis if disease is syphilis; Tube 4, to show that antigen is not hemolytic, should show no hemolysis.

While this method appears simple, it does not stand critical analysis. Noguchi[20] has studied it and found it impractical for the following reasons:

1. Human complement requires for complete hemolysis ten times as much amboceptor as an equivalent amount of guinea-pig complement.

2. Human complement is less sensitive to fixation than that of guinea-pigs.

3. The quantity of human complement varies greatly, from one to three, with different samples of sera. If it were present in excess it would destroy a positive reaction; hence to be accurate each serum would have to be titrated for complement content before applying the test. Dilution would vary the amount of cells present which, aside from the labor involved, would destroy the value of the reaction.

4. If human complement is used there is no way of telling if antigen alone is antihemolytic.

5. Old samples of blood could not be used because complement rapidly deteriorates, and the cells undergo spontaneous hemolysis after a time so that controls could not be kept from day to day.

Boas[21] condemns the method because active serum is employed.

IV. NOGUCHI COMPLEMENT DEVIATION METHOD

Noguchi has devised a plan of using an anti-human hemolytic system. In his recently published results[18] he presents a large series of observations from which it appears that his method is more delicate than the original Wassermann. Instead of the hemolytic series being sheep's cells and hemolytic serum from rabbits, he uses human red blood cells, with anti-human serum from rabbits. In this way he hopes to eliminate the

20. Noguchi, H.: Proc. Soc. Exper. Med. and Biol., 1909, vi, 77.
21. Boas, H.: Berl. klin. Wchnschr., 1909, xlvi, 400.

great variability in the amount of hemolytic amboceptor present in a given serum. In other respects the method is one of complement deviation in which the five factors used are separate, can be accurately measured, and any of them tested, should this be necessary, to control the work. The cells used are in the proportion of one drop of blood to four cubic centimeters of normal salt solution. They are not washed, but well shaken to insure a uniform emulsion.[22] One cubic centimeter of emulsion is used in each tube and this is added before the first incubation. The serum to be tested is employed in the amount of one drop from a capillary pipette. At times two drops may be used, but as this amount is often found to be antihemolytic, Noguchi recommends one drop. This serum is not inactivated. As complement 0.04 c.c. of fresh guinea-pig serum is employed; as hemolytic amboceptor, two units of the serum of a rabbit immunized to human red blood cells. The titer of such serum must be over 0.01 c.c. for one unit. As antigen 0.3 per cent. solution of impure lecithin in equal parts of absolute alcohol and normal salt solution, or alcoholic extract of syphilitic livers, one drop from a capillary pipette, is used. In making this test I have followed the Noguchi protocol, with two added controls (Tubes 7 and 8).

PROTOCOL III.—NOGUCHI METHOD.

	Test for Diagnosis.	First Control Set. Known Syphilitic Serum.	Second Control Set. Known Non-Syphilitic Serum.	Third Control Set. Without Serum.
	Tube 2.	Tube 4.	Tube 6.	Tube 8.
Control tube without Antigen for each test.	a. Patient's serum.	a. Positive serum.	a. Normal serum.	
	b. Human blood suspension.	b. Human blood suspension.	b. Human blood suspension.	b. Human blood suspension.
	c. Complement.	c. Complement.	c. Complement.	c. Complement.
	Tube 1.	Tube 3.	Tube 5.	Tube 7.
Determinative tubes containing Antigen.	a. Patient's serum.	a. Positive serum.	a. Normal serum.	
	b. Human blood suspension.	b. Human blood suspension.	b. Human blood suspension.	b. Human blood suspension.
	c. Complement.	c. Complement.	c. Complement.	c. Complement.
	d. Antigen.	d. Antigen.	d. Antigen.	d. Antigen.

Incubation at 37 C. for 1 hour.*
Antihuman hemolytic amboceptor to all tubes.
Incubation at 37 C. for 2 hours. Let stand at room temperature over night.

* For incubation a water-bath was used instead of a thermostat. This insures a more constant temperature of the surrounding medium, and brings the solution to the required temperature sooner.

Tubes 2, 4, 6, 8, 5 and 7 should be hemolyzed. No hemolysis should be seen in 3, and if the case is syphilitic, Tube 1 should show the same

22. Noguchi now advises that the cells be washed by allowing the emulsion to stand over night, pouring off the clear supernatant solution and adding fresh salt solution up to the original volume. (Personal communication.)

inhibition. It can readily be seen that this method is much simpler than the Wassermann technic. The cells are always easily obtained in the quantities needed and no centrifuge is necessary to wash them. Inactivation of the serum is not required, as the complement in the serum, as well as any mixed with the cells, is supposed to be absorbed during the first incubation period.

In order to render the method more available to persons without the facilities of organized laboratories, Noguchi prepared the different reagents by impregnating filter paper with amboceptor, complement and antigen in the proper quantities. He has shown[23] that complements and opsonins when dried at 23 C. retain their activity for a long time, and even withstand heating to 100 C. Immune bodies are even more resistant to the effects of desiccation. Where guinea-pigs are not readily obtained he recommended the use of dried complement, but suggested that when this serum could be obtained fresh it would be better to use it in the strength of 0.04 c.c.

This simplification renders the method very attractive, but before it can be accepted it must be thoroughly tried, and controlled by a method which has gained the most universal acceptance, such as the Wassermann technic.

A question which comes up in connection with Noguchi's method is that of isohemolysins. The work which has been done lately in hemolysis in cancer has called attention to the presence of isohemolysins in the blood in a number of diseases. Eisenberg[24] has demonstrated isohemolysins in five out of eight cases of syphilis. Weil[25] found hemolysis of alien cells in one out of two cases of lues. The proportion of cells and serum in such experiments is different from that used in the serum diagnosis test, and no foreign complement is added in the cancer test, but the presence of isohemolysins must be considered and might mask certain weakly positive reactions just as the existence of anti-sheep amboceptor masks the complement absorption in certain of the Wassermann reactions. Noguchi has suggested that the tubes be carefully observed for evidence of hemolysis at the end of the first incubation period, and if this is found, the case might be considered one of malignant disease. This has been done in all my tests with evidence of such hemolysis only three times. It has been noted, however, that a few of the cases of carcinoma showed quite rapid hemolysis after the hemolytic

23. Noguchi, H.: Jour. Exper. Med., 1907, ix, 462.
24. Eisenberg: Quoted by Weil. Jour. Med. Research, 1908, xix, 281.
25. Weil, R.: Jour. Med. Research, 1908, xix, 281.

amboceptor had been added, such hemolysis taking place before that in the control tubes. Occasionally this phenomenon has been noted in the tubes containing serum from syphilitic patients which gave a positive Wassermann reaction. This masking of the syphilitic antibody explains the failure to obtain positive results in a small percentage of the syphilitic sera. In such cases, with the method of collecting the patient's blood, it was impossible to repeat the test accurately with the patient's own cells; but it would seem wise in practice always to use the patient's own cells in applying this reaction. This would necessitate multiplying controls, but for the sake of accuracy such a method should be adopted.

The two factors, antigen and amboceptor, dried on paper, have differed in the time they can be kept. The antigen has been found to be somewhat unstable. The first lot furnished me, which at the beginning was perfectly satisfactory, at the end of five weeks gave no reaction with strong luetic serum. When, however, two pieces of such samples were used good results were obtained. This shows that in one month the antigen in this form had lost one-half its potency, although it was kept in the dark in a tighly stoppered bottle. A second lot of material retained its power for a longer time, but at the end of two months failed to react with weak sera. This variability in the strength of dried antigen suggests the advisability of keeping in stock an alcoholic solution and preparing the papers frequently, or of using the liquid in definite measured quantities. The hemolytic amboceptor, on the other hand, has retained its power in dried form for at least three months. Samples made three months ago and kept in stoppered dark-colored bottles still contain two units and react in a perfectly satisfactory manner.

In my study of the Noguchi reaction, hemolytic amboceptor prepared on filter-paper by the originator of the method has been used. Antigen prepared in a similar manner was used in the first 400 cases, but on account of the variability of this form, an alcoholic extract of syphilitic liver has lately been substituted.

All material, except complement and syphilitic liver extract, has been obtained from the originator of the method, who desired to see if such material would prove as satisfactory in other hands as in his experience.

In nearly all of the tests I have used my own blood for red blood cells in order to have that factor as nearly constant as possible. In about fifty cases parallel controls with the patient's blood as indicator have been run, and in no case did I find any difference in the results.

The result of the comparison of the Wassermann and Noguchi methods are given in Tables 3 to 9 inclusive.

TABLE 3.—WASSERMANN AND NOGUCHI REACTIONS IN PRIMARY, SECONDARY, AND TERTIARY SYPHILIS

No.	Time Since Appearance of First Symptoms.	Present Manifestations.	Treatment.	Wassermann.	Noguchi.	Remarks.
			PRIMARY SYPHILIS.			
18	Five weeks.	Ulcerated chancre, adenopathy.	None.	+	+	
68	Two weeks.	Chancre, inguinal adenopathy.	None.	++	++	
79	Seven weeks.	Chancre, adenopathy.	None.	++	++	
88	Eight weeks.	Chancre, inguinal adenopathy.	None.	+	+	
152	Not stated.	"Indurated ulcer," adenopathy.	None.	—	—	
153	Two weeks.	Chancre, adenopathy.	None.	+	+	
240	One week.	Mixed sore, adenopathy.	None.	—	—	Developed roseola three weeks later.
245	Three weeks.	Chancre, adenopathy.	None.	++	+	
190	Two weeks.	Chancre, adenopathy.	None.	++	+	Repeated after two weeks injection, same result.
358	Four weeks.	Chancre, adenopathy.	None.	++	++	
397	Two weeks.	"Indurated ulcer," adenopathy.	None.	+	+	
457	Two weeks.	Chancre, adenopathy, alopecia.	None.	++	++	
466	Eleven weeks.	Chancre, inguinal adenopathy.	None.	++	+	
485	Not known.	Chancre, inguinal adenopathy.	None.	++	++	
456	Two weeks.	Chancre, adenopathy.	None.	—	—	
492	Three weeks.	Chancre, adenopathy.	None.	+	+	Same as case 456, taken one week later
			SECONDARY SYPHILIS.			
1	Two months.	Roseola.	Six inunctions.	++	+	
2	Three months.	Roseola.	Twelve inunctions.	++	+	
5	Not known.	Maculopapular.	None.	++	++	
13	Eighteen months.	Nodular syphilide of face.	Six weeks, pills.	++	+	
17	Six months.	Papular.	Three months, pills.	+	+	
33	Five weeks.	Roseola.	One injection, Hg. biniodid.	++	++	
34	Two months.	Roseola.	One injection, Hg. biniodid.	+	+	
37	One year.	Condylomata of anus.	Three months, irregular.	+	+—	
47	Two months.	Roseola.	None.	+	++	
48	Not known.	Roseola.	None.	—	+	
49	Ten months.	Papular.	Three months, protoiodid pills.	++	++	
56	Not known.	Miliary papular.	Six inunctions.	++	++	
58	Five weeks?	Roseola.	None.	++	++	
61	Five months.	Condylomata of anus.	Not known, "little."	++	++	
67	Six months.	Syphilid of tongue.	Four months.	+	+	
76	Not known.	Roseola.	None.	++	++	
89	Not known.	Roseola.	Nine injections, Hg. biniodid.	++	+	
103	Four months.	Maculopapular, iritis.	Six weeks, bichlorid pills.	+	+	
106	Three months.	Maculopapular.	None.	+	+	
107	Five months.	Not stated.	Three months, pills.	+	+	
109	Three months.	Papular, iritis.	Eighteen inunctions.	++	++	
113	Six weeks.	Roseola.	None.	++	++	
135	Five months.	Iritis.	Four months.	+	+	
143	Denied.	Condylomata of anus.	None.	—	+	
149	Three years.	Not stated.	Two months.	—	+	
161	Six weeks.	Roseola.	None.	++	++	
162	One year.	Papular.	Six months, none for six months.	+	—	
166	Three weeks.	Roseola.	None.	++	++	

No.	Time Since Appearance of First Symptoms.	Present Manifestations.	Treatment.	Wassermann.	Noguchi.	Remarks.
168	Not known.	Roseola.	None.	++	++	Roseola masked by scabies.
180	No known.	Roseola.	None.	++	++	
192	One year.	Syphilid of tongue.	Ten months.	++	+—	
196	Three months.	Rash, jaundice, aortic diastolic, murmur.	"Little."	++	++	
204	Two years.	Conjunctivitis.	"Fair."	+	++	
218	Two months.	Chancre of lip, papular eruption.	Three injections, Hg. salicylate.	++	++	Repeated after six more injections, Wassermann +, Noguchi ++.
236	Denied.	Papular.	None.	++	++	
241	Four months.	Mucous patches in mouth.	Ten weeks, pills.	—	—	Bauer reaction, ++.
257	Two months.	Roseola, herpes progenitalis.	One injection, Hg. salicylate.	++	++	Primary lesion, probably herpetic.
260	Four months.	Not stated.	Six weeks.	++	++	
261	Six months.	Papular, iritis.	Poorly.	—	++	Cannot tolerate mercury.
269	Three months.	Papular.	Poorly.	++	++	
287	Three years.	Iritis.	None.	++	+	
323	Six months.	Papular.	Four months.	++	++	
325	Two months.	Maculopapular.	Five weeks.	++	++	
326	Three months.	Not stated.	None.	++	++	
330	Three weeks.	Chancre of lip, maculopapular.	None.	++	++	
331	Nine years?	Papular.	Poorly.	++	++	
335	Four months.	Mucous patches in mouth.	Six weeks.	++	++	
336	Five months.	Papular.	Two weeks.	++	++	
349	Two months.	Roseola.	None.	++	++	
353	Three months.	Roseola.	None.	++	++	
354	Two months.	Papular.	None.	++	++	
356	Two months.	Roseola.	Two weeks.	++	++	
357	Three months.	Maculopapular.	Two weeks.	++	++	
379	Six weeks.	Roseola.	One injection, Hg. salicylate.	++	++	
382	Six weeks.	Roseola.	None.	++	++	
400	Five months.	"Ill-defined eruption."	Little.	++	++	Had marked scabies mixed with other eruption.
404	Three months.	Roseola.	Little.	++	++	
412	Four months.	"Rash" nephritis.	Little.	+	+	
418	Eight months.	Papulopustular of face.	Two months.	++	++	
421	Three weeks.	Roseola.	None.	+	++	
426	Three months.	Maculopapular.	Two weeks, protolodid pills.	++	++	
432	One month.	Roseola.	"Little."	++	++	
433	Two months.	Maculopapular.	One week.	++	++	
451	Two months.	Roseola.	One week.	++	++	
460	Six weeks.	Roseola.	Three weeks, protolodid pills.	++	+	
487	Not known.	Roseola, angina.	None.	++	++	
488	Not known.	Papular, chancre of finger?	None.	—	++	
496	Denied.	Papular.	None.	++	++	
497	Denied.	Papular.	Little.	++	++	
499	Denied.	Keratitis, myositis.	None.	+	+	Bauer ++.
523	Denied.	Squamous lesions of palms, mucous patches.	None.	++	++	
525	Three weeks?	Papular.	One week.	++	++	
526	Two and one-half years.	Papular.	One year, mixed.	+	+	No treatment for past year.
527	Two years.	Nodular.	Eight months, pills.	++	++	
528	Eight months.	Papular.	One month.	++	++	
531	Two months.	Papular.	Two weeks, protolodid pills.	++	++	

TERTIARY SYPHILIS.

No.	Time Since Appearance of First Symptoms.	Present Manifestations.	Treatment.	Wassermann.	Noguchi.	Remarks.
8	Two and one-half years.	Serpiginous.	Two and one-half years.	+	+	Very resistant to treatment.
12	Thirty years.	Gumma of leg.	Six months, irregular.	++	+	
29	Not known.	Gumma of face.	Irregular.	+	+	
45	Not known.	Gumma of lip.	Fair.	++	++	
75	Four years.	Serpiginous.	Poorly.	+	++	Patient very alcoholic.
77	"Several years."	Serpiginous.	Irregular.	—	+—	
82	Nine years.	Gummata of legs.	Poorly.	+	++	
85	Forty-eight years.	Leucoplakia of tongue.	Fair.	+	+	Has epithelioma developing on leucoplakia.
86	Denied.	Serpiginous.	None.	+	+	
102	Denied.	Syphilitic glossitis.	None.	—	—	
144	Not known.	Serpiginous.	Five weeks, mixed.	+	+	
146	Fourteen years.	Gummata of legs.	Irregular.	—	+	
164	Fourteen months.	Serpiginous.	Fourteen months.	—	—	
165	Not known.	Serpiginous.	Poorly.	—	+	Bauer +.
173	Not known.	Serpiginous.	None.	++	++	
184	Fifteen years.	Squamous lesion of sole of foot.	About four years in all.	+	+—	
204	Seven years.	Serpiginous.	Poorly.	++	+	
220	Fifteen months.	Gumma of palate.	Seven weeks.	++	+	
221	Thirty-five years.	Gummata of legs.	Irregular.	++	+	
235	Twenty years.	Not stated.	Little.	++	++	
256	Four years.	Serpiginous.	Little.	++	++	
264	Eight years.	Serpiginous.	Eighteen months, intermittent.	++	—	
265	Not known.	Gumma of neck.	Three weeks.	++	—	
324	Three years.	Gumma of penis.	Three months, mixed.	—	+	Did not respond to mixed treatment but healed under local applications.
328	Two years.	Gummata of penis and legs.	Irregular.	++	++	
329	Two and one-half years.	Gummata of scalp.	Two years, continuous.	++	+	
345	One year.	Syphilitic glossitis.	One year, continuous.	—	—	
352	One year.	Gumma of testicle, serpiginous of leg.	Six months.	++	+	
355	Four years.	Syphilid of tongue.	Four months.	—	—	
367	Denied.	Gummata.	None.	++	++	
378	Ten years.	Serpiginous.	Six months.	++	+	
399	Twenty-eight years.	Gummata of legs.	Three months, irregular.	++	+	
402	Four years.	Serpiginous.	Six months.	++	++	No treatment for three years.
403	Four years.	Gumma of foot.	Intermittent, poorly.	++	++	Has had three relapses.
406	Three years.	Not stated.	Little.	++	++	
423	Six months?	Gumma of leg.	Four months, intermittent.	++	++	
429	Denied.	Gumma of palate.	None.	++	++	
435	Denied.	Gumma of leg, edema of foot.	None.	++	++	
450	Denied.	Gummata of scalp.	One year, KI.	+	++	No treatment for three years.
458	Denied.	Gumma of forehead.	Three weeks, mixed.	++	++	
476	Fifteen years.	"Scaling lesions."	Three months in all.	++	++	
481	Denied.	Serpiginous.	None.	++	++	
486	Seven years.	Serpiginous and gumma.	Five months' injection, Hg. salicylate.	++	++	
520	Four years.	Gumma of foot.	One year mixed.	++	++	
537	Eight years.	Interstitial glossitis.	About six months.	++	++	No treatment for seven years.

TABLE 4.—WASSERMANN AND NOGUCHI REACTIONS IN LATENT SYPHILIS

LATENT SYPHILIS

No.	Time Since Infection.	Treatment.	Wassermann.	Noguchi.	Remarks.
133	One year.	None.	++	++	
234	Not known.	None.	+	+—	Mother of child with congenital syphilis.
246	One year.	None.	++	++	Now has alcoholic neuritis.
370	Denied.	None.	—	—	Has typical syphilitic scars and perforation of palate.
7	Two years.	Nine weeks, mixed.	—	+	
25	Six months.	Ten weeks.	+	++	
41	Denied.	Eight weeks.	—	—	Had squamous syphilid of palm which has disappeared under treatment.
54	Six months.	Six months.	+	+—	
60	Four months.	Three months injection, Hg. salicylate.	+	—	One month later developed frontal periostitis.
87	Three years.	Eleven months, irregular.	+	+	
95	Several years.	Little.	+	+	Autopsy later showed tuberculosis, patient gave history of syphilis.
132	Twenty-five years.	Six months at beginning of disease.	—	—	
136	Not known.	Three months, mixed.	+	+	Had gumma of arm three months ago.
151	Four months.	Thirty-six inunctions.	+	+	
160	Not stated.	Six months.	—	—	
222	Eleven months.	Five months.	+—	+—	
243	Eight months.	Little.	—	—	
244	Denied.	Three months, mixed.	—	—	Had squamous syphilid of palm which has disappeared under treatment.
259	Six months.	Five injections, Hg. salicylate.	++	++	
337	Seven months.	Six months.	++	+	
348	Ten years.	Thirteen injections.	—	—	Has headaches at night, is very neurotic.
368	Eighteen months.	Little.	++	++	
388	Twelve years.	Little.	—	—	
407	Twelve years.	Not known, little.	—	—	
416	Fifteen months.	Fifteen injections, Hg. salicylate. Ten months, protoiodid pills.	+	—	

No.	Time Since Infection.	Treatment.	Wassermann.	Noguchi.	Remarks.
424	Twenty years.	Sixteen months, mixed.	++	++	Miscarriage with syphilitic fetus twenty years ago. Had syphilitic periostitis two months ago.
436	Five months.	Sixteen injections, Hg. salicylate.	—	—	Had syphilitis periostitis two months ago.
448	Three months.	Seven injections, Hg. salicylate.	+	++	
455	Four months.	Two months, protiodid pills.	+—	+—	
473	Denied.	Three months, mixed.	++	+	Had gumma of leg five months ago.
477	Fourteen months.	One year, protiodid pills.	++	+	
489	Denied.	Little.	+—	+	Bauer +.
494	One year.	Seven months, protiodid pills. Four months, mixed.	+—	+	Bauer ++.
495	Eight months.	Seven months, bichlorid pills.	+	++	
514	Five months.	Fourteen injections, Hg. salicylate.	—	—	Had positive Wassermann four months ago.
521	Nine months.	Seven months, "pills."	++	++	
522	Forty years.	Eight months, mixed.	++	++	Had gumma of elbow eight months ago.
529	Six months.	Six injections, Hg. salicylate. Four months, protiodid pills.	+—	+—	
534	Twenty years.	"Little."	—	—	Bauer —.
23	Eighteen months.	Seventeen months.	—	+	
30	Eighteen months.	Seventeen months.	—	+—	
32	Two and one-half years.	One year, injections.	—	+—	
44	Not known.	Eight months, mixed.	—	+—	
50	Ten years.	One year.	—	—	No treatment for nine years.
52	Eighteen months.	Eleven months.	—	+—	
80	One year.	Eleven months.	—	+	
130	Three years.	Eighteen months.	—	—	No treatment for eighteen months.
147	Twenty-five years.	Two years.	+	+—	No treatment for twenty-three years.
213	Eight years.	Two years, mixed.	+	+	
34A	Two years	Two years.	—	—	Treatment stopped.
34B	Two years, two months.	Two years.	+	+	Same as 34A; treatment stopped two months ago.
249	Sixteen years.	Seven months, mixed, lately; some before.	—	+	
16A	Three years.	One year, continuous; some before.	—	—	Treatment stopped.

16B	Three years, two months.	One year, continuous; some before.	++	++	Same as 16A; treatment stopped two months ago.
289	Twenty-two years.	"Fair."	—	+	
293	Seventeen months.	One year.	—	+	
9	Three years.	Three years.	+	+	Hemiplegia one year ago.
24	Four years.	Three years.	—	—	No treatment for past year.
53	Eight years.	Three years.	+—	+	
111	Twelve years.	Five years.	—	—	
127	Eleven years.	Four years.	+—	+	No treatment for seven years.
129	Twenty years.	Three years, total.	+	—	Had gumma of testicle one year ago.
157	Thirteen years.	Well.	—	—	
233	Twelve years.	Two years, nine months, total.	—	—	Relapse one year ago; continuous treatment since.
254	"Several years."	"Well."	—	+	
266	Nine years.	Eleven courses, extending over two years.	—	—	
271	Twelve years.	Three years, continuous; four years, intermittent.	++	+	
274	Twelve years.	Three years.	+—	+	
333	Three years, three months.	Three years, injections and inunctions.	+	+	Negative reaction three months ago; test made by Dr. Noguchi. No treatment for past two months.
334	Two years, five months.	Two years, five months.	—	—	
359	Seventeen years.	Four and one-half years, intermittent.	+—	+	Had many relapses, last one nine months ago.
395	Denied.	Two and one-half years, injection, Hg. salicylate.	—	—	Had symptoms of spinal cord syphilis which have disappeared under treatment.
419	Twenty years.	Well.	++	++	Now has melancholia.
425	Eleven years.	Four years.	—	—	
449	Nine years.	Five years, continuous.	—	—	No treatment for six years.
459	One year, nine months.	One year, eight months.	+—	+—	
461	Twelve years.	Seven courses, irregular.	+	+	Had several relapses.
463	Twelve years.	Nearly continuous for twelve years.	++	++	Very resistant to treatment.
465	Two years.	Two years, protiodid pills.	++	+	
475	Six years.	Six years, pills.	++	++	
480	Twenty years.	Irregular.	—	+	
490	Thirty years.	Fairly well.	—	—	
515	Three and one-half years.	Sixty injections, two years, mixed.	+—	+	
530	Six years.	Three years, pills; eight months, injections, twenty inunctions.	+—	+—	
536	Two years.	Sixty inunctions, one year protiodid pills.	++	++	

TABLE 5.— WASSERMANN AND NOGUCHI REACTIONS IN VISCERAL SYPHILIS

Number.	History of Infection.	Diagnosis.	Symptoms.	Treatment.	Wassermann.	Noguchi.	Remarks.
10	2 years ago	Teno-synovitis	Swelling and tenderness	14 months	—	+	
40	7 years ago	Hemiplegia	Paralysis	Not known	+	+	
65	5 years ago	Periostitis	Pain and irregularity over tibiæ.	Poorly	+	+	
73	Denied	Hepatitis	Jaundice, enlarged liver	None	+	+	
81	Denied	Gumma of tibia	Tumor over tibia	None	+	+	Improved on KI. X-ray showed gumma-like shadow.
117	Denied	Cerebrospinal syphilis	Not stated	Fair	+—	+	
118	20 years ago	Aortic valvular disease	Aortic regurgitation	6 injections Hg. salicylate.	+	—	
119	Denied	Cerebrospinal syphilis	Not stated	6 mos. injections Hg. salicylate.	+—	+	Is improving under treatment.
137	25 years ago	Syphilis of spleen	Tumor of spleen, enlarged glands.	1 year at beginning.	+	+	Clinical diagnosis favored syphilis.
140	Chancroids(?) 9 years ago.	Arterial sclerosis	Not stated	Little	+	+	
158	Denied	Meningeal syphilis	Headaches at night, irregular pupils.	None	+	+	
176	Probably by husband.	Not stated	"Many surgical operations."	None	—	—	Husband had syphilis 9 years ago; now has general paralysis.
181	Indefinite.	Syphilitic hepatitis	Enlarged liver	Fair	++	+	
182	23 years ago	Aortic valvular disease	Aortic regurgitation	Not stated	—	—	
187	Denied	Hemiplegia	Paralysis, aphasia	Not stated	+	+—	Rapidly improved under antisyphilitic treatment.
188	"Warts" 10 years ago.	Syphilitic spinal paralysis.	Paralysis	50 injections Hg. salicylate.	+—	—	5 years ago, facial paralysis; 3 years ago, stiff pupils.
193	20 years ago	Aneurism of aorta	Not stated	Not stated	—	—	
195	Denied	Aortic valvular disease	Aortic roughening	Not stated	+	+—	Bauer +.
202	Denied	Syphilitic orchitis	Enlarged testicle	Not stated	—	—	Bauer —. Histologic examination of testicle showed spirochæte.
211	30 years ago	Hemiplegia	Paralysis	1 month	—	—	Patient 60 years old.

215	Indefinite.	Aneurism of aorta	Not stated	Not stated	—	—	Bauer —.
216	Indefinite.	Aortic valvular disease	Aortic regurgitation	Not stated	—	—	
178	Denied.	Disseminated sclerosis	Not stated	None	+—	+—	Spinal fluid showed weak reaction
226	Denied	Optic atrophy	Blindness	Not stated	+—	+	Bauer +—. Noguchi globulin test +.
227	Denied	Gumma of clavicle	Tumor over clavicle	None	++	++	
229	Indefinite	Cerebral syphilis	Not stated	Not stated	—	—	
247	Sore 20 years ago	Aortic valvular disease	Aortic regurgitation	6 months	—	+	No history of secondaries.
280	4 years ago	Arthritis	Pain and swelling of knee	6 months	—	—	
281	Denied	Hemiplegia	Paralysis	None	++	+—	Patient 26 years old. Improved under KI.
284	Indefinite	Sclerosis of cord	Ataxia, increased reflexes	None	++	+—	
291	Denied	Cerebral syphilis	Headaches, worse at night	None	+—	—	
300	"One miscarriage"	Cerebral syphilis	Headaches, worse at night	None	—	+	
310	1 year ago	Hemiplegia	Paralysis	1 week	++	++	
311	14 years ago	Myelitis	Not stated	4 months	+	+	
319	Denied	Syphilitic periostitis	Pain and irregularity over tibia	None	++	++	
341	1 year ago	Chronic arthritis	Pain and swelling of knee	Little	++	++	
351	13 years ago	Hemiplegia	Paralysis	Not known	++	++	
362	"Several miscarriages."	Syphilitic osteomyelitis	Chronic sinuses	None	++	+	Infection probably placental. Had chronic sinuses in several places not benefited by surgical treatment.
371	8 years ago	Pachymeningitis or tabes	Spastic gait, partial paralysis	3 mos., irregular	—	++	Bauer —. Amount of serum used contained 5 units of hemolysin for sheep cells, enough to mask 1 unit of syphilitic antibody.
375	Probably by husband.	Ocular palsy	Blindness	Much in past 2 years.	—	—	
387	Sterility	Aortic valvular disease	Aortic regurgitation	Not stated	—	—	
389	Probably congenital.	Syphilitic encephalitis	Progressive spastic diplegia	None	+—	+	Child 3 years old.
389½	Denied	Syphilitic encephalitis	Headaches, Jacksonian epilepsy.	Not stated	+	++	
398	Denied	Syphilitic orchitis	Enlarged testicle	None	++	—	

TABLE 5.—WASSERMANN AND NOGUCHI REACTIONS IN VISCERAL SYPHILIS.—Continued

Number.	History of Infection.	Diagnosis.	Symptoms.	Treatment.	Wassermann.	Noguchi.	Remarks.
408	Indefinite	Cerebrospinal syphilis	Not stated	Not stated	−	+	
409	Denied	Syphilitic iritis	Failing vision	Little	++	++	
417	4 years ago	Gumma of testicle	Enlarged testicle	2 years, irregular	++	++	
414	Denied	Syphilitic periostitis	Pain and swelling over tibia	None	++	++	
427	25 years ago	Hemiplegia	Paralysis, aphasia	Not stated	+	+	
440	Chancroid (?) 20 years ago.	Hemiplegia	Paralysis, systolic murmur at apex.	Not stated	+−	−	
441	Denied	Paraplegia	Weakness, weakness of bladder.	Considerable mixed.	+−	−	
442	Denied	Paraplegia	Paralysis, weakness of bladder	Little	++	++	
453	Denied	Not stated	Ataxia	Considerable	−	−	Acute ataxia 10 years ago cleared up under antisyphilitic treatment.
479	11 years ago	General arthritis	Arthritis	None	++	++	
500	Denied	Syphilitic periostitis	Pain and swelling over tibiæ	None	++	++	
503	Denied	Syphilitic hepatitis	Enlarged liver, jaundice	None	−	−	Bauer +. Serum hemolytic to human erythrocytes.
504	"Many years ago."	Aortic valvular disease	Headaches, aortic roughening	Not stated	−	−	Bauer +−.
506	Denied	Syphilis of cord	Atrophy of tongue, pain in legs	None	+−	+	Bauer +.
510	Denied	Hemiplegia	Gradual paralysis, ankle clonus, no Babinski.	None	+−	+	Bauer +.
518	25 years ago	Syphilitic meningitis	Feeling of pressure	Full treatment	+−	+−	Bauer; not enough native hemolysin.

TABLE 6.—WASSERMANN AND NOGUCHI REACTION IN TABES AND GENERAL PARALYSIS

No.	History of Infection.	Treatment.	Wassermann.	Noguchi.	Remarks.
		TABES			
28	Seven years ago.	Well.	—	+	Disease apparently stationary.
38	Ten years ago.	Continuous for past seven months.	+—	+—	
125	Thirty-one years ago.	One month.	+—	+	
126A	Twenty years ago.	Poorly until lately.	—	—	
126B	Twenty years ago.	None for past five weeks.	+	+	Same as 126A; treatment stopped to see if reaction would appear.
141	Twenty years ago.	Not stated.	—	+	
156	Thirteen years ago.	Continuous for past four years.	—	+	No treatment until tabes appeared four years ago.
183	Sore thirty years ago; no secondaries.	Not stated.	—	—	Well marked Charcot joint.
186	Seven years ago.	Fifteen injections Hg. salicylate, lately.	+	+	
189	Denied.	None.	—	—	Bauer —.
210	Denied.	Thirty-six injections, Hg. salicylate.	+	+	Had gumma of leg six months ago.
212	Denied.	None.	—	—	Tabetic symptoms not well marked.
232	Denied.	None.	++	++	
250	Fifteen years ago.	Two months.	+—	++	
292	Denied.	Not stated.	++	++	
296	Twelve years ago.	None.	+	+	
302	Twenty-nine years ago.	None.	++	—	
303	Eight years ago.	None.	—	++	
304	Denied.	None.	+	+	
305	Twelve years ago.	Ten months.	+	—	
306	Fourteen years ago.	Not known, considerable.	—	+	
307	Eighteen years ago.	None.	++	—	
308	Twenty-five years ago.	None.	—	++	
309	Thirty-five years ago.	None.	—	+	
312	Eighteen years ago.	None.	—	—	
313	Several years ago.	Not stated.	+	+	
343	Urethritis, followed by secondaries.	None.	++	+	
350	Denied.	None.	—	—	
366	Nineteen years ago.	Two years.	+—	++	Also has aortic valvular disease.
369	Denied.	None.	—	—	
410	Twelve years ago.	None.	+	—	
413	Twenty years ago.	Four months injections, Hg. salicylate.	+	+	
420	Eighteen years ago.	Not stated.	—	++	
439	Twenty-three years ago.	Thirty injections Hg. salicylate, lately.	+—	+	
509	Twenty-one years ago.	Many injections in past year.	++	++	Also has aortic valvular disease.
517	Denied.	None.	—	—	Now has colon bacillus sapremia.
532	Denied.	None.	++	++	
535	Twenty-two years ago.	Not stated.			
		GENERAL PARALYSIS			
120	Denied.	None.	+	+	Marked lymphocytosis in spinal fluid.
124	Denied.	None.	—	+	Early in the disease.
474	Denied.	None.	++	++	Symptoms well marked.

TABLE 7.—WASSERMANN AND NOGUCHI REACTIONS IN CONGENITAL SYPHILIS

No.	Age.	Symptoms.	Treatment.	Wassermann.	Noguchi.	Remarks.
154	Three years.	Idiocy, anemia, enlarged liver, frontal bosses.	Little.	+	++	Can not tolerate mercury.
225	Eight years.	Deafness, Hutchinson's teeth, jaundice, chorea.	Little.	++	+	
234	Ten years.	Saddle nose, Hutchinson's teeth, frontal bosses.	None.	++	++	Eight brothers and sisters died in infancy. Father has optic atrophy.
237	Ten years.	Congenital keratitis.	None.	++	+	

TABLE 8.—WASSERMANN AND NOGUCHI REACTIONS IN SPINAL FLUID FROM SYPHILITIC PATIENTS

No.	Diagnosis.	History of Syphilis.	Evidence of syphilis.	Wassermann.	Noguchi.	Remarks.
91	Tuberculous meningitis	Several years ago.	Old specific scars.	+	+	
98	General paralysis.	Seven years ago.	Not stated.	—	—	
117	Cerebrospinal syphilis.	Denied.	Not stated.	—	—	Blood positive one month earlier.
165	Uremia, syphilis secondary.	Not obtained.	Rash.	—	—	Patient died of uremia next day.
178	Disseminated sclerosis.	Denied.	Not stated.	+—	—	Blood showed weak positive reaction.
315	Congenital syphilis?	Not reported.	"Rash that looks specific."	—	—	From child five months old.
316	Congenital syphilis?	Not reported.	"Rash that looks specific."	—	—	From child six months old.
84	Congenital syphilis.	Not reported.	Anemia malnutrition, enlarged liver, rash.	+	—	From child three months old.

TABLE 9.—WASSERMANN AND NOGUCHI REACTIONS IN BLOOD AND SPINAL FLUID FROM AUTOPSIES

BLOOD SERUM

No.	Anatomical Diagnosis.	Evidence of Syphilis.	Wassermann.	Noguchi.	Remarks.
63	Mitral valvular disease.	No other.	+—	+—	
219	Aortic valvular disease; syphilitic hepatitis.	Aortic disease, cirrhosis of liver.	++	+	
344	"Syphilis."	Rupial lesions.	+	—	
374	Tuberculosis, chronic pulmonary; aortitis; pericarditis; chronic nephritis.	Aortitis, cutaneous syphilid.	+	—	

SPINAL FLUID—SYPHILITIC

139	Syphilis, visceral.	Syphilitic pneumonia, chronic myocarditis; syphilitic cirrhosis of liver, interstitial orchitis.	—	++	
185	Syphilitic meningitis.	Marked thickening of pia.	+	+	
201	Aortic valvular disease.	Thickening of aortic valves.	—	—	Fluid removed five days; postmortem.
294	Pneumonia; syphilitic aortitis.	Aortitis.	—	—	
364	Tuberculosis, chronic pulmonary; syphilitic hepatitis.	Hepatitis, cutaneous syphilid.	—	++	

SPINAL FLUID—NOT SYPHILITIC

251	Pneumonia; granular ependymitis.	None.	—	—	
252	Carcinoma of pylorus.	None.	—	—	
253	Hemorrhage, cerebral; arterial sclerosis.	None.	—	—	
295	Tuberculosis, chronic pulmonary; softening of pons.	None.	—	—	
317	Internal hydrocephalus.	None.	—	—	

Primary, secondary, tertiary, latent, visceral and congenital syphilis are tabulated, as also tabes and general paralysis. To these are added the results of the examination of spinal fluids of syphilitics obtained by lumbar puncture during life and of spinal fluids and blood obtained at autopsy. The tabulation is arranged to show clearly any difference in results by the two methods. When a difference was found at first examination the reaction was repeated to control the methods and only the final result is published.

Summarized the results are given in Table 10.

TABLE 10.—SUMMARY OF COMPARISON OF WASSERMANN AND NOGUCHI METHODS.

Stage.	Total Number.	Wassermann. Positive. No.	%	Wassermann. Negative. No.	%	Noguchi. Positive. No.	%	Noguchi. Negative. No.	%
Primary	16	13	81	3	19	13	81	3	19
Secondary	76	70	92	6	8	74	97	2	3
Tertiary	45	37	80	8	20	40	88	5	12
Latent, (none or little) treatment	39	25	64	14	36	25	64	14	36
Latent, fairly well treated	46	21	46	25	54	27	60	19	40
Visceral	60	41	68	19	32	40	66	20	34
Tabes	38	22	55	16	45	26	68	12	32
General Paralysis	3	2	67	1	33	3	100	0	0
Congenital	4	4	100	0	0	4	100	0	0
Autopsy, blood	4	4	100	0	0	2	50	2	50
Autopsy, spinal fluid	5	1	20	4	80	3	60	2	40
Spinal fluid from syphilitic patients	8	3	37	5	63	1	12	7	88

These results show that the Noguchi modification in 5 to 20 per cent. of the cases was more delicate.

With the spinal fluids the Wassermann method seems to give a better result, as is also the case with the blood obtained at autopsy. The number of postmortem bloods, however, is so small that definite conclusions can not be made, but that this material is satisfactory for the Wassermann reaction has been demonstrated by Pick and Proskauer,[26] and Fraenkel and Much.[27] The latter, however, found that the blood of scarlet fever obtained from the cadaver gave in five out of twelve samples a positive reaction.

CONTROLS

In the course of this work a very large number of control bloods have been examined with negative results by both methods. These may be classified according to the nature of the illness under the headings: "Dermatologic," "Medical," Surgical" and "Neurologic." The four groups include ninety-one bloods and sixteen spinal fluids, as follows:

Blood Controls, Dermatologic.—Acne vulgaris, 4; pityriasis versicolor, 1; dermatitis herpetiformis, 2; pyogenic dermatitis, 1; eczema, 3; erythema multiforme, 2; fibroma molluscum, 1; ecthyma, 1; furuncu-

26. Pick, L., and Proskauer, A.: Med. Klinik, 1908, iv, 539.
27. Fraenkel, E., and Much, H.: München. med. Wchnschr., 1908, lv, 2479.

losis, 1; herpes zoster, 1; impetigo contagiosa, 1; lupus vulgaris, 1; lupus erythematosus, 1; lichen planus, 1; rosacea, 2; pemphigus, 1; syphilophobia, 1; tuberculosis verrucosa cutis, 1; chronic ulcer of mouth, 1.

Blood Controls, Medical.—Arthritis deformans, 2; adiposis dolorosa, 1; bronchitis, 1; hepatic cirrhosis, 2; diabetes mellitus, 1; diphtheria, 1; fever (unexplained), 1; cerebrospinal meningitis, 1; tumor of lung, 1; tuberculosis, 7; varicella, 1; meningitis (variety not stated), 1; chronic cardiac disease, 1.

Blood Controls, Surgical.—Suppurative adenitis, 1; balanitis, 1; chancroids, 9; carcinoma, 11; condyloma acuminatum, 1; gonorrhea, 3; traumatic orchitis, 1; tumor of chest, 1; chronic ulcer of leg, 4.

Blood Controls, Neurologic.—Cerebral tumor, 3; hemiplegia, 4; headaches, 3; spastic paraplegia, 1; paraplegia, 1; vertigo, 1.

Spinal Fluid Controls.—Tuberculous meningitis, 9; cerebrospinal meningitis, 1; meningitis (variety not stated), 3; gastroenteritis with meningeal symptoms, 2; alcoholic cerebral edema, 1.

The controls which gave a reaction may be divided into three classes: (A) scarlet fever, (B) leprosy and (C) miscellaneous.

A. The frequent occurrence of a positive reaction in scarlet fever has been much discussed and, as the etiology of scarlet fever is unknown, has aroused some conjecture as to whether or not a spirochete may be concerned in the causation of this disease. Much and Eichelberg[28] report as positive, 50 per cent. of the scarlet fever bloods which they examined. Halbertstaedter, Müller and Reiche[29] report five out of ten cases, and Butler,[30] four cases, positive. On the other hand, many others report they have never obtained the reaction in this disease. My results are given in Table 11, where it may be seen that in eight cases of scarlet fever the Wassermann method gave positive results in 12 per cent. and the Noguchi in 37 per cent.

B. Leprosy has been studied with the Wassermann technic by various observers. The most extensive observations are by Jundell, Elmkvist and Sandman,[31] who studied twenty-six cases, of which four gave the reaction. Of the four positive cases, three were of the tubercular and one of the maculo-anesthetic type. My results are shown in Table 12.

28. Much, H., and Eichelberg, F.: Med. Klinik, 1908, iv, 671.
29. Halbertstaedter, L., Müller, E., and Reiche, A.: Berl. klin. Wchnschr., 1908, xlv, 1917.
30. Butler, W. J.: New York Med. Jour., 1909, lxxxix, 207.
31. Jundell, I., Almkvist, A., and Sandman, F.: Centralbl. f. inn. Med., 1908, xxix, 1181.

TABLE 11.—WASSERMANN AND NOGUCHI REACTIONS IN SCARLET FEVER

Number.	Day of Disease.	Wassermann.	Noguchi.
197	7th	—	—
198	7th	+	+
199	5th	—	—
200	5th	—	++
262	6th	—	—
263	8th	—	—
278	6th	—	—
279	3d	—	+

TABLE 12.—WASSERMANN AND NOGUCHI REACTIONS IN LEPROSY

No.	Form of Disease.	Wassermann.	Noguchi.	Remarks.
258	Mixed.	+	++	Marked general adenopathy.
327	Tubercular.	—	—	Repeated with same result.
405	Maculo-anesthetic.	—	++	Repeated with same result, but negative with inactivated serum.

TABLE 13.—OTHER CASES NOT SYPHILITIC GIVING A POSITIVE REACTION

No.	Diagnosis.	Wassermann.	Noguchi.	Remarks.
21	Arthritis deformans.	—	+	Also done by Dr. Noguchi with same result.
22	Arthritis deformans.	—	+	Also done by Dr. Noguchi with same result.
93	Varicella; congenital syphilis?	+	+	Probably has congenital syphilis. Evidence: Malnutrition, notched teeth, frontal bosses.
169	Tuberculosis verrucosa cutis.	—	+—	Diagnosis confirmed by histologic examination.
208	Chancroids; eczema.	—	+—	Had chancroids one year ago; no secondary symptoms.
231	Dilatation, chronic cardiac.	—	+—	One clinical diagnosis was acute aortitis. All venereal disease and symptoms denied.
273	Leucoderma.	—	++	Boy; no further evidence of syphilis.
338	Normal man.	—	+	Father of boy with brain tumor; denies all symptoms of venereal disease.
340	Amyotrophic lateral sclerosis.	—	++	Foreigner, in whom history was difficult to obtain.
381	Carcinoma of penis, before operation.	—	+	Microscopic examination confirmed diagnosis.
381	Same case after operation.	—	+	Negative with inactivated serum.
482	Generalized dermatitis.	—	+	Negative with inactivated serum.
483	Erythromelalgia; arterial sclerosis.	—	+	Negative with inactivated serum; denies all evidence of syphilis.
384	Epileptiform attacks.	—	+	Negative with inactivated serum.
506	Nephritis; chronic uremia.	—	++	Negative with inactivated serum.
516	Monoplegia.	—	+	Negative with inactivated serum; no history of syphilis; had gonorrhea several years ago.
519	Traumatic arthritis.	—	+	Negative with inactivated serum; patient has general adenopathy; no other specific symptoms.
524	Herpes progenitalis.	—	+	Negative with inactivated serum; had herpes four weeks ago; no other specific symptoms.

Of three cases, one gave the Wassermann, two the Noguchi reaction. With the Wassermann method inhibition was only partial, while with the Noguchi it was complete.

C. We now come to a class of cases, the miscellaneous group, which are of the utmost importance in the determination of the reliability of this test. These are summarized in Table 13.

Among these, only one gave the Wassermann reaction. This patient was a boy with varicella who presented strong evidence of congenital syphilis. No family history pointing to syphilis could be obtained and, unfortunately, the case disappeared from observation so that the test could not be repeated after the varicella had subsided. Hence it could not be accurately determined whether this disease was the cause of the reaction or not. Two cases of arthritis deformans gave a positive Noguchi reaction; this is of interest in that Noguchi has found that his test frequently gives inhibition in this disease. In most of the other cases giving the reaction the blood was sent for diagnosis, the clinician suspecting syphilis in each case, but having little evidence to substantiate this diagnosis. Syphilis could not be absolutely excluded in any instance.

Noguchi ascribes great importance to the various grades of reaction. Complete or marked inhibition he regards as diagnostic, while slight inhibition he considers as an indication for further treatment in those cases in which the diagnosis of syphilis has previously been made. The seventeen cases (No. 381 is considered as one) reported in Table 13 show three with complete and eleven with marked inhibition, or a total of fourteen diagnostic reactions. This number of positive results in non-syphilitics would appear to be too high for unconditional acceptance of the method.

The cause of the increased sensitiveness of the Noguchi method is apparently due to two factors: First, a small antibody content is not masked by the presence of a large amount of native hemolysin; second, the serum used is not inactivated. Sachs[32] last year called attention to the fact that active serum gave a stronger reaction than inactive, but that with such serum positive reactions were obtained in non-syphilitic individuals. Boas[21] reported similar results and has shown that active serum is two to four times more powerful than inactive, and that the reaction appears earlier and persists longer with active serum. He further presented a list of forty-five non-syphilitics giving a positive reaction with active serum, but reacting negatively when the same serum was inactivated. From his work he concludes that it is not safe to employ active serum, and condemns the Tschernogubow method because such serum is

32. Sachs: Verhandl. d. deutsch. Dermat. Gesellsch. X Kong., 1908, p. 167.

used. Application of such observations and deductions to the study of the Noguchi method leads to the conclusion that both the increased number of specific reactions and the few non-specific ones are due to the use of active serum. This does not destroy the value of the Noguchi method, because inactive serum can readily be employed instead of active. Referring to Table 13 it will be noted that the last eight cases gave results corresponding to the Wassermann reaction when inactive serum was used. In these tests the active serum was employed in the amount of one drop, which corresponds to 0.02 c.c. With the inactive serum 0.08 c.c. was used, the proportion of human serum to guinea-pig serum being two to one, the same as is employed in the Wassermann reaction. I believe the use of active serum explains the non-specific reaction with the Noguchi method in some cases and am now working on this phase of the question. The results of such work will shortly be published.

When one compares the different methods, the advantages of Noguchi's technic make it most attractive. The small amount of serum required, the ease of preserving the reagents, and the fact that one does not require a constant supply of sheep's blood, are important points in its favor, but to put it into the hands of untrained workers seems to me most undesirable. Good controls are needed for each test, and the more that are introduced the more accurate are the results. Only those having special training in hemolytic work and serum diagnosis can appreciate the difficulties of such a complicated method. To obtain reliable results the work should be done under favorable conditions by one who has been trained in laboratory methods. To place the material in the hands of inexperienced workers would bring the method into disrepute, for results would be too uncertain. The enormous responsibility assumed by one in making a diagnosis would seem to require at least as much experience as is expected of a bacteriologist or clinical laboratory worker.

CONCLUSIONS

1. The Wassermann reaction is a fairly definite diagnostic measure. A positive reaction practically always means syphilis. Negative findings give only presumptive evidence of the absence of syphilis.

2. The Bauer modification is not reliable because of the inconstant content of native hemolysin to sheep cells. A large anti-sheep hemolytic content will mask a partial complement fixation.

3. The Noguchi reaction is more readily applied and the materials are more easily procured and kept than with the Wassermann method. It is also more sensitive than the Wassermann reaction. This increased sensitiveness, however, sometimes causes a positive reaction with non-

specific sera which give a negative Wassermann reaction. Experiments now under way seem to indicate that this may be avoided by the use of inactive serum.

I wish to express my thanks to Dr. Noguchi for instruction in the technic of the original Wassermann method, for placing the technic and materials for his method in my hands, and also for controlling in large part the early portion of my work.

The clinical material for this work has been obtained through Dr. Fordyce, who placed the cases in the dermatologic department of the College Clinic and in his wards at the City Hospital at my disposal, also through Dr. Van der Poel, of the genitourinary department, Drs. Stevens and Barringer, of the out-patient department of Bellevue Hospital, and Drs. Norris and Crowell of the pathologic staff of Bellevue Hospital. To these gentlemen, as well as to Dr. R. J. Wilson, of the Willard Parker Hospital, and to Drs. Joseph Collins, I am deeply indebted.

THE MUCH-HOLZMANN SERUM REACTION IN INSANITY *

A. J. ROSANOFF, M.D.
KINGS PARK, N. Y.

While the present trend in psychiatry seems to be mainly in the direction of psychogenic causes in the etiology of the so-called functional insanities, yet from time to time cases are reported or in other ways facts are brought to light which would indicate that the toxic theory of the origin of these conditions is, at least for the present, not to be definitely discarded.

In a brief preliminary communication published a short time ago[1] H. Much describes a new serum reaction which he found to be almost specific for dementia præcox and manic-depressive insanity. This reaction is based on the alleged power possessed by the serum in cases of these conditions of inhibiting the hemolytic action of cobra venom on human red blood corpuscles.

With the collaboration of W. Holzmann he examined the blood in four hundred cases, including, on the one hand, various forms of insanity and, on the other hand, many different physical diseases without mental disturbances, and found this reaction always present in cases of manic-depressive insanity and dementia præcox, regarded as such in the strictly limited classical sense, according to Kraepelin; he also found it in some cases of epilepsy with periodically recurrent mental disturbances; further, he found it in sane persons belonging to families in which insanity existed.

These remarkable results led me to apply this reaction in a series of cases of various forms of insanity at the Kings Park State Hospital, and, for the purposes of control and comparison, in a number of normal persons.

The technic of the reaction, as described by Much and Holzmann, is as follows: 0.35 c.c. of serum is mixed with 0.25 c.c. of a 1:5000 solution of cobra venom; to this is added 0.5 c.c. of a 10 per cent. suspension of human blood corpuscles (prepared by allowing blood to flow into normal salt solution containing 2 per cent. of sodium citrate, washing the cor-

* I am indebted to Dr. H. Noguchi, of the Rockefeller Institute for Medical Research, for the impulse to apply the Much-Holzmann reaction in the cases cited in this paper and for invaluable assistance in making the hemolytic tests.

1. Much, H.: Eine Reaktion im Blute von Geisteskranken. München med. Wchnschr., May 18, 1909.

puscles twice with normal salt solution and finally making a suspension of the desired strength); this mixture is placed in the incubator for two hours and then in the refrigerator for twenty-two hours, at the end of which time the reading is taken.

I have found it convenient to modify the technic to a slight extent. The stock solution of cobra venom was prepared in the manner suggested by Much and Holzmann, namely, by making a 2 per cent. solution of the dried venom in distilled water and then adding an equal volume of glycerin; this solution was preserved by the addition of a few drops of chloroform and was further protected against putrefaction by being kept in the refrigerator. For use it was diluted with normal salt solution until a solution of the strength of 1:5000 was obtained. The cobra venom which I used was from a specimen in possession of Dr. H. Noguchi of the Rockefeller Institute; by titration this specimen of venom was found to be so actively hemolytic that the relative quantity of the solution employed in the reaction had to be reduced to a little over one-half of that employed by Much and Holzmann. The proportions of the other ingredients in the reaction—serum and suspension of blood corpuscles—were not changed, but their absolute quantities were reduced in order to avoid taking unnecessarily large quantities of blood.

From 1 to 1.5 c.c. of blood taken from the lobe of the ear supplied the amount of serum which I used in the reaction, namely, 0.2 c.c.; to this was added 0.08 c.c. of the 1:5000 solution of cobra venom and 0.3 c.c. of blood corpuscle suspension. In the control tubes 0.2 c.c. of normal salt solution was used in place of serum.

Complete hemolysis occurred in the control tube almost always before it occurred in any of the other tubes, so that it became evident that practically all serums had some slight power of inhibiting the hemolytic action of cobra venom on human blood corpuscles. On the other hand, complete inhibition of hemolysis did not occur in a single instance. Thus the reaction became merely a test of the relative degree of this inhibiting power possessed by a given serum. Therefore, I took the readings, as suggested by Much and Holzmann, at the end of twenty-four hours (two hours in the incubator and twenty-two hours in the refrigerator), on thoroughly shaking the tubes. In taking the readings in this way I found no difficulty in distinguishing between a strongly positive reaction and a distinctly negative one; but in many instances of moderate inhibition of hemolysis I was unable to make the distinction satisfactorily; for this reason, in tabulating my findings, I counted as positive (+) all cases in which the mixture in the tubes on shaking showed complete

opacity, as slightly positive or doubtful (±) all cases in which there was opacity with a distinct laked appearance, and as negative (—) all cases in which the tubes showed any degree of transparency.

The cases used in this investigation were carefully selected from the large amount of such material that is available at this hospital with a view to excluding all but perfectly typical cases in which the diagnoses were as nearly certain as possible; thus in all the cases of general paresis the clinical diagnosis had been corroborated by lumbar puncture. To this there were, however, five exceptions: in four cases there were symptom-complexes resembling manic-depressive insanity, but running a chronic course with no remissions or alternating phases; these cases form in the table of findings a separate group designated "chronic psychoses allied to manic-depressive insanity"; and one case, which presented a clinical picture of dementia præcox, showed, in addition, some evidences of organic brain disease, and appears in the table as "psychosis allied to dementia præcox."

The specimens of serums assumed to be normal were obtained from officers and employees at this hospital, who kindly consented to give some of their blood not only for the purpose of furnishing the serum, but also for preparing the suspension of blood corpuscles used in the reaction. I take this opportunity of acknowledging my indebtedness to them.

As will be seen from the figures in the table, the serums of some of the apparently normal persons showed a positive reaction. The statement of Much, to the effect that this reaction may be found in the serums of sane persons belonging to families tainted with insanity, has already been referred to. I regret to have found it impracticable to inquire into the matter of insane heredity in my cases. The following table shows my findings:

TABLE 1.—MUCH-HOLZMANN REACTION

Mental Disorders.	Total No.	+	±	—
Dementia præcox	38	22	2	14
General paresis	35	5	3	27
Epilepsy with insanity	12	2	4	6
Polyneuritic psychosis	8	1	1	6
Manic-depressive insanity	15	0	1	14
Involution melancholia	10	1	0	9
Senile dementia	11	0	1	10
Arteriosclerotic brain disease	6	0	3	3
Infantile cerebral palsy	5	1	2	2
Paranoic condition	2	0	0	2
Cerebral syphilis	1	0	0	1
Chronic phychoses allied to manic depressive insanity	4	2	1	1
Psychosis allied to dem. præc.	1	0	0	1
No psychosis	37	3	5	29

In 109 of the above cases the serum was examined also for the Wassermann reaction. In order to determine whether there is any relationship between the Much-Holzmann reaction and the Wassermann reaction I have tabulated my results.

TABLE 2.—MUCH-HOLZMANN AND WASSERMANN REACTION

Wassermann Reaction.	No. of Cases.	Much-Holzmann Reaction. +		±		—	
		No.	%	No.	%	No.	%
+	26	8	30.8	2	7.7	16	61.5
±	13	1	7.7	2	15.4	10	76.9
—	70	12	17.1	10	14.3	48	68.6

SUMMARY OF FINDINGS

1. Practically all human serums possess the power, in a more or less pronounced degree, of inhibiting the hemolytic action of cobra venom on human blood corpuscles.[2]

2. A comparatively high degree of this power, which constitutes the basis of Much and Holzmann's reaction, is not strictly specific for any psychosis, being found with greater or less frequency in almost all psychoses and in the blood of a considerable percentage of persons who are apparently normal (8.1 per cent. in the series cited in this paper).

3. This reaction was present in more than half of my series of cases (57.9 per cent.) of dementia præcox. As it appears to be much more common in this condition than in any other, it may prove to be a diagnostic aid; it would seem that the presence of this reaction in a psychosis should add, in the consideration of the diagnosis, some degree of probability in favor of dementia præcox.

4. Of a series of fifteen typical cases of manic-depressive insanity not one gave a positive reaction, and in only one was the reaction doubtful, being clearly negative in all the rest. I might add here that two of the patients had recovered from their psychosis when their blood was examined.

5. There is apparently no relationship between the Wassermann reaction and the Much-Holzmann reaction.

---

2. For a complete presentation of the subject of venom hemolysis see Noguchi: Snake Venoms, chap. xvi (published by the Carnegie Institution, Washington, D. C., 1909).

CHRONIC INFECTIOUS ENDOCARDITIS*

FRANK BILLINGS, M.D.
CHICAGO

Bacteriemia now is recognized readily by means of blood cultures and a blood culture in febrile patients has come to be a not unusual routine in many hospitals. The technic is so simple that it may be successfully done at the bedside in private practice and the culture media may be transported a considerable distance to the laboratory. With a sharp hypodermic needle the blood may be withdrawn from a prominent subcutaneous vein without noteworthy pain or danger. The blood culture enables one to recognize more readily the infectious character of the disease. With an infection proved, the interpretation of the physical and clinical phenomena becomes rational. On this a definite diagnosis may be made and the prognosis becomes more certain. The treatment necessarily becomes more definite, rational and conclusive.

Before the use of blood cultures infectious endocarditis, termed malignant, ulcerative, etc., was sometimes recognized during life by the signs of local heart lesions, petechial spots of the skin, emboli of larger vessels, splenic enlargement and tenderness, microscopic and sometimes macroscopic hematuria, subcutaneous, often painful, reddish nodules, a not infrequent cough with or without bloody sputa, a septic temperature, sometimes very mild, at other times severe, rapid heart action, and, finally, a failing heart with dyspnea, cyanosis and death.

Every practitioner, especially if he has opportunities for hospital observation, has seen many patients suffering from what he believed to be infectious endocarditis, but has been unable to prove the diagnosis during life, and frequently a postmortem was not permitted.

In the patients who suffer from an infectious endocarditis implanted on an old lesion the clinical phenomena which are present even when first seen are those of broken heart compensation. There may be a septic temperature of moderate degree. The pulse may be that of ordinary broken heart compensation. There will be evidences of a widely dilated heart, cyanosis, a swollen, tender liver and more or less anasarca. The infectious nature of the condition could not be positively recognized without a blood culture.

---

* Read in the Section on Practice of Medicine of the American Medical Association at Atlantic City, June 8-11, 1909.

Since blood cultures have been practiced the literature abounds in reports of infectious endocarditis, both chronic and acute. In many instances reports are made of cases in which the infectious organism was demonstrated during life by blood cultures, and in many others the inference is made that the disease was an infectious endocarditis because of the symptoms and the clinical course, but no positive evidence is furnished by blood cultures or by postmortem.

The series of cases on which this report is based have been proved by blood cultures made in all but one instance during life to be of infectious type. In one the bacterium was obtained immediately after death by paracentesis of the heart and the culture grown from the blood so obtained.

Only one acute case is included in this series and that one because it affords means of comparing the clinical course of the acute with that of the so-called chronic cases.

Osler[1] gives a classical description of chronic infectious endocarditis with a report of a series of ten cases. In the majority of the cases reported by Osler the disease extended over a long period; the shortest four months and the longest thirteen months. As stated by him, the disease may be manifested by a slight feverish condition only and may be prolonged for weeks or months. I think other symptoms usually are present, but escape notice because no definite observations are made of such patients. The cases are often mistaken for colds or beginning tuberculosis, and for various other conditions which are often thought to be simple and unimportant. Many suffer from chills of varying severity, coming on at irregular times and followed by fever and sweat. It is not strange, therefore, that malaria is considered the cause in many instances, and quinin may be given for a considerable period of time without benefit.

In infectious endocarditis, especially of the chronic type, occurring in those patients who have not suffered from a chronic valvular disease or other anatomical lesion of the heart, the symptoms may be mild, like those given by Osler and observed by many clinicians.

In the series of fourteen cases presented in this report the disease manifested itself clinically over varying periods of time. In one patient (Case 1) the symptoms began two years before the real condition was recognized. Case 8 began fourteen months before a definite diagnosis was made. Patient 13 probably suffered from the disease for more than two years, and in the earlier part of the illness the diagnosis of typhoid fever

1. Osler, W.: Quart. Jour. Med., 1909, ii, 219.

was made for a condition which was, in all probability, infectious endocarditis; the diagnosis having been based on the fact that there was fever and splenic enlargement. No rose spots were found, however, there was no diarrhea, and the Widal reaction was negative throughout. The shortest clinical course was that in Case 5, and even in this there is doubt whether the infection did not occur long before. Because of the long clinical course of many of the cases one is justified in the term "chronic infectious endocarditis."

Another important characteristic of such patients is the fact that they are ambulatory in many instances. Patient 7 unquestionably suffered from an infectious endocarditis for more than a year before she finally became bedridden and during that time traveled extensively. She was ill, as manifested by a poor appetite, languor, nervousness and a slight rise of temperature. Patient 6 was a student in a university when the clinical course evinced important illness, and for two months after leaving the university, while she remained ill, she was up and about and finally traveled by rail for the consultation, when her real condition was recognized. Patient 8 traveled from Iowa to Chicago suffering from dyspnea on exertion, general weakness, nervousness, palpitation of the heart, and so forth, and had been in a condition quite as bad, from the account given by her, for a year. Patient 10 was ill for three months before his condition was recognized, and in that interval traveled extensively and was off on a vacation, hunting and fishing.

While the disease did not produce conditions severe enough to force the patient to go to bed, yet if any one of these patients had been under daily observation there would undoubtedly have been found physical evidences of the disease sufficient to have required bed treatment.

I have personally studied the fourteen cases included in this report. The number could be made much larger by the inclusion of cases seen but once, or under conditions which did not permit of study of the patients or of the causative bacteria. The infectious organism found in these fourteen cases was as follows: [2]the pneumococcus (eleven cases): streptococcus (three cases). The large proportion of patients suffering from pneumococcus infection as compared with streptococcocus infection is noticeable, even in so small a group of cases. This especially is true when compared with the report by Dr. Thomas J. Horder on Infective

2. During the period of time covered by this report cases of acute infectious endocarditis due to staphylococcus (one case), gonococcus (one case) and streptococcus (two cases) have been seen but are not included because of the acute clinical course.

Endocarditis.[3] In his report the number suffering from pneumococcemia was less than one-third of those suffering from streptococcemia.

In communicating with clinicians in various cities I find that they report streptococcus infection of the endocardium to be much more prevalent or frequent than pneumococcus infections. Dr. E. C. Rosenow[4] has made the bacteriologic investigations in these patients. He has already made a report[5] on the cultural characteristics and the results of animal experiments with the pneumococcus found in these patients.

The organisms obtained in the eleven patients suffering from pneumococcemia had many of the morphological characteristics of streptococci. Study of the organisms in culture and in animals proved that they were the pneumococcus. In the three patients included in this series the study of the organism which was called the streptococcus was not afterward made as in the other patients, and it is the belief of Dr. Rosenow that, had the organism of these three patients been studied as in other cases, all would have proved to be the pneumococcus.

PNEUMOCOCCUS CASES: CHARACTERISTICS OF ORGANISMS ISOLATED FROM THE BLOOD OF THE ELEVEN PATIENTS OF THIS SERIES

The cocci all produced fine colonies in blood-agar plates surrounded by a variable zone of greenish discoloration. Hemolysis did not occur. When grown in isolated colonies on the surface of the blood-agar slants they all had a greater or lesser tendency to adhere tightly to the surface. The more chronic the case and the later in the course of the disease the organism was isolated, the more marked was this tendency of the organism to adhere to the surface of the medium.

Unlike the ordinary pneumococcus found in pneumonia, the organism grows readily in the fibrin clot of the broth of the blood culture in large clumps or colonies. The fluid portion often remains perfectly clear for twenty-four to forty-eight hours, after which time a diffuse or flocculent cloudiness appears, and an abundant sediment, which consists of masses or clumps of bacteria, precipitates. The organism is Gram-positive, usually is not surrounded by a capsule, and, when grown in broth or litmus milk, it forms diplococci with many very long conglomerate chains.

---

3. Hordes, T. J.: Quart. Jour. Med., ii, 289, 1909.

4. The Dane Billings Fellow in Medicine in Rush Medical College and a worker in research in the Memorial Institute for Infectious Diseases, Chicago.

5. Rosenow, E. C.: Jour. Infect. Dis., vi, 245, 1909.

In the beginning it usually ferments inulin slowly, but this property soon is lost.

After cultivation on artificial media, usually it promptly loses the property of adhering to the surface, and later ceases to grow in chains and reverts to the characteristics of the typical pneumococcus. On passage through animals it often reverts very promptly to the type which is characteristic of the ordinary pneumococcus.

When first isolated they were all freely susceptible to phagocytosis in normal blood, and also in the patient's blood.

Cultures from all patients show a characteristically low grade of virulence to animals. Before the tendency to adhere to the surface is lost a primary injection of a huge dose intraperitoneally, intravenously or subcutaneously, or in all three places at once, is apt to produce endocarditis and pericarditis, but not peritonitis or subcutaneous abscesses. The tendency to produce endocarditis and pericarditis is very striking in all the animal experiments, quite regardless of the point of inoculation.

After the tendency to adhere to the surface is lost huge doses are practically never fatal, nor is endocarditis or pericarditis produced by the inoculation unless combined with injury of the endocardium, and then only rarely. Instead of rendering the animal more resistant to subcutaneous injections, as is the rule with the pneumococcus, injections of the modified strain render the animal more susceptible. After the second or subsequent injection several things may happen. First, the animal may die in a few days of a pneumococcus. The culture from the dead animal's heart blood resembles ordinary virulent pneumococci. Second, pericarditis and endocarditis, or pericarditis alone, may occur; and the characteristics of the organism obtained from the dead animal more nearly resemble those of the inoculated bacterium than of the ordinary pneumococcus. Third, in two instances, after two and three weeks respectively, the animals died of pneumonia, and the isolated organism from the dead animal resembled typical pneumococci.

This description corresponds in some respects with the statement made by Dr. Horder[6] in which a typical form of streptococcus is described by Dr. H. Thursfield.

It is to be hoped that others may study the streptococcal forms obtained from the blood in infectious endocarditis and other conditions as has been done by Dr. Rosenow. It may result in the establishment of the fact that the pneumococcus is the most frequent infective agent in endocarditis.

---

6. Horder, T. J.: Quart. Jour. Med., ii, 300, 1909.

THE SOURCE OF INFECTION

This may in some instances be satisfactorily learned. In one patient of this series the infectious endocarditis followed pneumonia. Tonsillitis had occurred in two. Alveolar abscesses occurred in two; grip occurred in one. In the other patients the source of infection could not be learned. There can be no doubt whatever that simple local infection, like tonsillitis, as well as abscesses of the aural cavities, infections of the postnasal space of the antra, and so forth, may be the port of entry.

In some patients of this series the infection was implanted on an old endocardial or valvular scar. An old heart lesion existed in seven patients, of whom six had suffered from rheumatic fever and one from chorea. Two of the patients gave no history and the question of previous heart lesion was in doubt. In five the infection had apparently been implanted on a normal endocardium or valve.

The valves involved in the fourteen cases were as follows: aortic valve alone, one; mitral alone, seven; pulmonary semilunar alone, one; aortic and mitral together, five; mitral and tricuspid together, one.

The evidence of heart lesion, as manifested by murmur, may be absent in the primary cases during the earlier part of the disease, and sometimes throughout it. Case 8 was examined by very competent physicians for months before the diagnosis was made and no heart murmur was heard. Case 10 had no murmur until about one month preceding death.

Pneumococcal inoculations with dead organisms were used with many of the patients and a careful study was made of the ordinary corpuscular elements of the blood, of the opsonic index, and of phagocytosis. It was found, among other things, that this organism apparently immunized itself against the antibodies of the host, a principle of infection first suggested by Prof. W. H. Welch. After inoculation leucocytosis was usually increased and phagocytosis was marked. The bacteriolytic power of the serum and of the leucocytes was, however, very low. The opsonic index was always increased by the injection. In some instances the temperature of the patient became lower after the inoculation, but the physical symptoms did not improve. In some patients, after inoculation with a large dose, the clinical course was aggravated in every way by the inoculation. In Case 10 the patient was inoculated several times with dead autogenous organisms with the usual results. When the patient was injected with normal serum intravenously, a sharp reaction followed, manifested by chill and fever, and the number of bacteria in the blood was much less for a period. No permanent benefit resulted from the

attempt to furnish complement by the injection of normal serum. Two of the patients suffering with streptococcus infection were injected with antistreptococcus serum: Patient 11 with two, and Patient 9 with many, injections without benefit.

The prognosis, with the present knowledge or want of knowledge in reference to any specific treatment, is, in my experience, bad.

The treatment should be absolute rest, with good air, sunshine, as much simple liquid and soft solid nourishment as may be given, and the use of those remedies which will conserve the patient's strength and the functions of the organs without too much mischievous interference. Inoculations of patients with large doses of their own dead pneumococci was always harmful. Observation of patients injected with even small doses (2,500,000) leads me to believe that this form of treatment for infectious endocarditis due to the pneumococcus is not only devoid of benefit to the patient but probably is harmful.

PROTOCOLS OF CASES

CASE 1.—D. R., male, single, aged 18, American, was admitted to the Presbyterian Hospital, Feb. 27, 1904; died March 31, 1904. Autopsy. Diagnosis: Chronic infective endocarditis, pneumococcemia, mitral stenosis and regurgitation.

History.—At 5 years old the patient had an attack of acute rheumatic fever; when about 10, a second attack of rheumatic fever. In the interval between the two attacks of rheumatism he was at times confined to bed with dyspnea and rapid heart action. During the second attack of rheumatism he was also troubled with dyspnea to the degree of orthopnea. From 11 to 15 years of age he was free from illness but noticed dyspnea on exertion. At 15 years of age he was confined to bed with an attack of weakness of the heart manifested by rapid heart action and dyspnea. The present illness began at about 16 years of age, that is, two years before the patient came under observation, with an attack of what was called grip. This seizure was ushered in with a cold in the head, anorexia, nausea and vomiting, shortness of breath and orthopnea. During the two years he has been constantly ill, confined to the bed most of the time, disturbed by nausea and occasional vomiting, rapid beating of the heart, dyspnea, more or less cough, and lately most of all if he attempted to exert himself, and also when he attempted to lie down. He was always most comfortable when sitting. No authentic history could be obtained of his pulse, temperature or respirations during this illness.

Examination.—On admission the patient showed marked pallor of the skin and mucous membranes. There was a slight blueness of the finger-nails and visible mucous membranes. The patient's general nutrition was below par. The tongue was grayish white; the tonsils somewhat enlarged and red. The respirations were increased but not labored. A marked precordial pulsation with systolic retraction was visible. There was one hazelnut-sized lymph gland in the left submaxillary region. No other lymph nodes were noticeably enlarged. Palpation over the chest showed a marked tremor in the region of the heart but no thrill. The left border of the heart extended 15 cm. from the mid-sternum, the right 5 cm. to the right of the sternal edge and the base was at the second costal cartilage. The apex-beat was in the sixth interspace just outside the nipple line. The heart action was rapid and of the gallop-rhythm type. Many heart pulsations did not reach the radial arteries. There was a loud musical systolic mur-

mur heard in the mitral area and also in the left axilla and over the left scapula. There was also a very rough presystolic murmur heard in the mitral area and toward the sternum. The pulmonic second tone was markedly accentuated. There was no pulmonary dulness. The breath sounds were harsh and numerous mucous râles are heard on both sides, especially at the bases. The abdomen was flat and the abdominal walls thin. The liver did not extend below the costal arch and the spleen was not palpable. There was no edema of the extremities. The urine was scant, heavy, contained much lateritious deposit with a trace of albumin and a few hyalin casts and many moderately motile bacilli. On March 1 a twenty-four collection showed 600 c.c., specific gravity 1.032, a trace of albumin, a few hyalin and granular casts and many urates.

Course of Disease.—The patient had a septic temperature ranging from 99.2 in the morning to 101 or 102 in the afternoon. He gradually became worse, compensation became broken and venous stasis gradually developed with edema of the lower extremities, transudation in the serous cavities of the abdomen and chest and coincidently greater cyanosis. A blood culture revealed the pneumococcus in pure culture. In the latter part of the patient's illness he became drowsy and finally passed into coma. Cough, which existed from the first, became worse and the sputum became blood-stained. Areas of dulness developed over the lungs indicative of infarcts. The blood examination showed 5,500,000 red cells, 95 per cent. hemoglobin and 25,000 leucocytes on admission, and the leucocytes remained high throughout the illness of the patient. The patient died on March 31, 1904, and an autopsy was made a few hours thereafter.

Anatomical Diagnosis.—Chronic mitral endocarditis with calcification and stenosis of the mitral orifice; chronic mural endocarditiis of the left auricle; fibrous adhesive pericarditis; acute vegetative aortic and tricuspid endocarditis; cardiac hypertrophy with dilatation, especially of the left auricle; recent pulmonary infarcts of both lungs; terminal pulmonary edema with abscesses in the right middle lobe; passive hyperemia of liver, spleen and kidneys; hydroperitoneum; left hydrothorax; general edema; right serofibrinous pleuritis; caseous tuberculosis of tracheobronchial lymph glands.

Cultures made from the heart's blood and vegetation on the aortic and tricuspid valves revealed the pneumococcus in pure culture.

Case 2.—Mrs. C. P., housewife, aged 22, was admitted to the Presbyterian Hospital March 5, 1904; died March 19, 1904. Autopsy. Diagnosis: infective endocartis, pneumococcemia, mitral stenosis and tricuspid insufficiency.

History.—Patient stated that she always had enjoyed a fair degree of health but had never been robust. Five years before coming under observation she suffered from an attack of grip, and from that time dated the beginning of her present illness. She never fully recovered her health and complained of shortness of breath on exertion, palpitation of the heart and general weakness. These symptoms gradually increased and for the past four months she had not been able to work. Edema occurred in the legs, which were more swollen during the day, and the face was swollen early in the morning. She suffered from a miscarriage four months before admission, and following this the edema appeared, with greater shortness of breath, which was aggravated on the slightest exertion. Cough had developed in recent time and was troublesome enough to keep the patient awake at night.

Examination.—On admission the patient sat propped up in bed. The face was flushed and there was a slight cyanosis of the skin and visible mucous membranes. Respirations were 30 to the minute. The throat was red and cyanotic but the tonsils were not enlarged. The resonance of the chest was normal and a few dry and moist râles were heard over both sides of the chest, especially at the end of deep inspiration. The apex-beat of the heart could not be seen but was

palpable in the fifth interspace just within the mammillary line. There was a faint systolic thrill. Dulness extended on the left 11 cm. from the midsternum to the second left rib above and to the right edge of the sternum on the right. There was a loud rough systolic murmur in the mitral area with a marked accentuation of the second pulmonic tone. The pulse was very small and rapid, 110 to the minute. The abdomen was full, the abdominal wall tense and tenderness existed over the upper portions. The liver and spleen could not be palpated. A soft edema of the lower extremities extended to the knees. The finger-nails were cyanotic and the finger-ends slightly clubbed. The blood examination showed, red cells, 5,100,000; hemoglobin, 92 per cent.; leucocytes, 8,300. Twenty-four-hour urine amounted to 400 c.c.; specific gravity, 1.014; urea, 3 per cent.; trace of albumin and a few hyalin and faintly granular casts. The patient's temperature was of a low septic type ranging from subnormal to about 99 in the morning to 100 to 102 in the afternoon. (See Chart 1.)

Course of Disease.—Gradually the heart inadequacy increased with greater dyspnea, cough and more marked evidences of venous stasis. On March 17 the patient complained of pain in the liver region which could be felt extending downward to the level of the navel and was markedly tender. A pleural friction was heard over the left lower lobe posteriorly. On March 19 a loud diastolic murmur

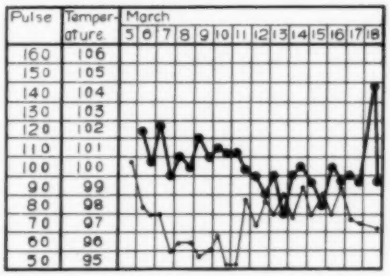


Chart 1.—Pulse and temperature curves in Case 2. Heavy line indicates pulse; fine line, temperature.

could be heard in the mitral area. A blood culture showed the pneumococcus in pure culture. The patient died on March 19, 1904, and an autopsy revealed the following:

Anatomic Diagnosis.—Mitral stenosis; vegetative tricuspid endocarditis; hemorrhagic infarcts and hyperemia of kidney, lungs, spleen and liver; hydropericardium; hydrothorax; anasarca; localized left fibrinous pleuritis.

Bacterial examination of the blood from the heart, from the lung infarcts and from the vegetations on the tricuspid valves revealed the pneumococcus in pure culture.

Case 3.—Miss A. S., aged 15, was admitted to the Presbyterian Hospital, May 6, 1904; died June 6, 1904. Diagnosis: infective endocarditis, pneumococcemia, mitral stenosis and regurgitation.

History.—Patient's previous health was good. In February, 1903, she suffered from an attack of pneumonia. She was confined to bed for a month and never regained her strength. During the last year she had not been able to work, and much of the time had been confined to bed because of general weakness, dyspnea on exertion and palpitation of the heart. All of these symptoms had increased gradually and recently the patient had coughed a great deal.

Examination.—On admission the patient's face was flushed, slightly cyanotic. The visible mucous membranes were cyanotic. The veins of the neck were slightly enlarged and pulsating. The whole anterior chest heaved with each heart-beat. The heart action was tumultuous and irregular. Respirations were rapid and labored. The lung resonance was practically normal with relative dulness posteriorly and below. The breath sounds were harsh, expiration prolonged and a few moist râles were heard over the dependent portions of the lungs. The heart extends to the left 18 cm. from the midsternum, to the second left rib above and 5 cm. from the right edge of the sternum. The apex impulse was diffuse in the sixth interspace outside the mammillary line. A distinct tremor could be felt over the apex impulse. A loud, rough, double murmur could be heard; the systolic murmur transmitted far to the left. The second pulmonary tone was much accentuated. A soft systolic murmur could be heard over the right fourth and fifth intercostal spaces. The abdomen was distended; the liver large, somewhat indurated and very tender. The spleen was not palpable. There was slight edema of the ankles and feet. Blood examination, 5,200,000 red cells, 100 per cent. hemoglobin, 15,000 leucocytes. Blood culture on admission was negative. On May 19 the leucocytes were 25,700, and a blood culture was negative. Urine on admission was scant, specific gravity 1.025; it contained a trace of albumin and a few hyalin and granular casts.

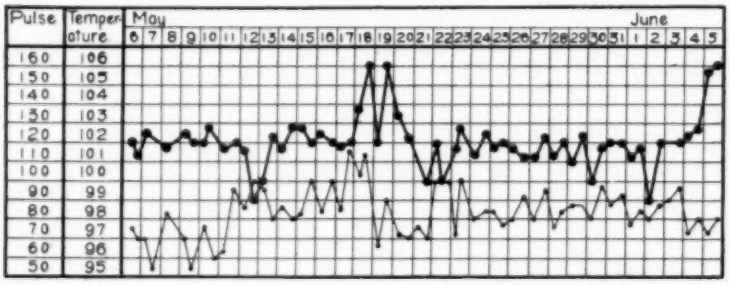


Chart 2.—Pulse and temperature curves in Case 3. Heavy line indicates pulse; fine line, temperature.

Course of Disease.—The temperature throughout was of a septic character. The patient grew rapidly worse, there were increasing evidences of heart inadequacy manifested by greater dyspnea and cyanosis; edema of the lower extremities gradually increasing to general anasarca; cough with bloody sputum and evidences of consolidation of a part of the right lower lobe. The patient died of exhaustion on June 6, 1904, and an autopsy was not obtained.

Puncture of the heart with precautions as to cleanliness was made immediately after death, and from the heart's blood a pure culture of the pneumococcus was obtained. The temperature throughout was of a septic character. (See Chart 2.)

CASE 4.—F. L., male, single, aged 16, Italian, admitted to the Presbyterian Hospital, Chicago, March 21, 1904; died April 13, 1904. Autopsy. Diagnosis: infective endocarditis, streptococcemia, mitral stenosis and aortic insufficiency.

History.—The patient said that his only previous illness was an attack of chorea which occurred six years before admission. Since that illness he had never been quite well and had suffered from dyspnea on exertion and some palpi-

tation of the heart. He had smoked cigarettes to excess until seven months before admission. The present illness dated, the patient thought, from the time he had chorea; but in spite of lessened strength and endurance, more or less palpitation of the heart and shortness of breath, he continued his work until one year before admission. Then these sysmptoms increased to such a degree that he was obliged to discontinue work. During the last year he had been confined to the house sitting in an easy chair or confined to bed. He had suffered a good deal from indigestion manifested by heaviness after meals and eructation of gas. A month before admission he noticed for the first time that his feet were swollen, and two weeks later this swelling rapidly extended to the thighs, then to the scrotum, and finally to the abdomen. He had had cough with some blood-streaked sputum, had been short of breath, especially on the least exertion and had noticed also a very rapid and throbbing heart action.

Examination.—On admission the patient is in orthopnea with rather marked dyspnea which was increased on the least exertion. The lips and skin were slightly cyanotic and pale. There was distinct pulsation of the distended veins in the neck. The general nutrition was poor. The lung resonance was practically normal and auscultation showed a few mucous râles distributed over both lungs, most numerous in the inferior portions. The apex-impulse of the heart could be seen just outside the nipple line at the fifth interspace. There was systolic retraction in the third and fourth left interspace. A distinct presystolic thrill could be felt to the left of the sternum with a distinct shock following the impulse of the heart. The heart dulness extended on the left 17 cm. from the midsternum, to the second left rib above and 3 cm. to the right of the sternum. A loud, rough, presystolic murmur and a rather soft blowing systolic murmur were heard in the mitral area. The systolic murmur was transmitted to the left axilla and scapula. The pulmonary second was accentuated. The radial pulse was rapid and weak. The abdomen was much distended. The liver was not palpable but marked tenderness existed below the right costal edge. The spleen was not palpable. Free fluid existed in the peritoneal cavity. There was marked edema in the lower extremities, of the external genitals and also of the lower abdominal wall. Blood cultures made on March 25 and again on April 7 were negative. On April 1, 1200 c.c. of serous fluid were withdrawn from the peritoneal cavity; it contained a preponderance of polynuclear leucocytes and was sterile. On admission the blood examination showed, red cells, 4,600,000; hemoglobin, 72 per cent.; leucocytes, 11,600.

Course of Disease.—On April 7 the leucocytes were 10,400. The urine was scant and remained so throughout the patient's stay in the hospital. In the many specimens examined there was a trace of albumin, a few hyalin and granular casts and occasionally a few red cells. The patient's temperature was of an irregular septic type ranging from normal to 103 but usually was from 99 to 100.5 in the morning and from 100 to 104.6 in the afternoon. Gradually the patient failed and died on April 13, 1904. The autopsy, made five hours after death, revealed:

Anatomical Diagnosis.—Stenosis of the mitral orifice; acute vegetative aortic endocarditis; cardiac hypertrophy and dilatation; localized fibrinous pericarditis; bilateral serofibrinous pleuritis; recent hemorrhagic infarct in upper lobe of right lung; pulmonary edema; hydroperitoneum; anasarca; passive hyperemia of liver, kidneys and spleen.

Blood cultures made from the heart's blood and vegetations on the aortic valves showed the presence of a streptococcus.

CASE 5.—S. N., male, single, aged 21, was admitted to the presbyterian Hospital, Chicago, April 23, 1907; died July 17, 1907. Diagnosis: infective endocarditis, pneumonia, mycotic aneurism and aortic insufficiency.

History.—On admission the patient stated that he had been well until three years ago. At that time he suffered from an acute polyparthitis with fever. He was not able to walk for two or three months. Following this he suffered from palpitation of the heart and shortness of breath upon exertion. At times there was pain in the region of the heart. Five months before admission the patient suffered from severe headache, general weakness and poor appetite. There was shortness of breath on exertion and he suffered from throbbing and rapid action of the heart. A month later, with the continuation of the symptoms, there occurred a dull pain in the palm of the left hand. This shifted soon to the left hip and soon afterward disappeared. About a month before admission the patient again suffered from pain in the left hip, knee and ankle and was treated for sciatica by a physician. Two weeks before admission this pain in the left hip became very severe and the sharpest pain was located just above the left hip joint and became constant. Since that time the pain had increased, had been throbbing in character and the hip had been very tender. During the last five months the patient had lost thirty pounds in weight.

Examination.—The patient lay on the right side; was very restless and appeared to be in great pain. His face was pale with a little cyanosis of the lips, finger-nails and visible mucous membranes. When he attempted to walk the pain

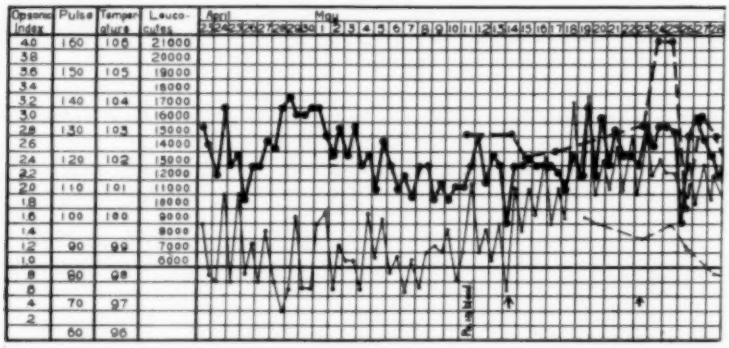
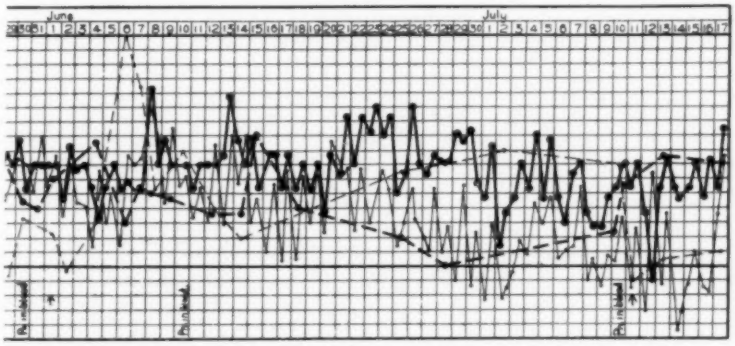


Chart 3.—Pulse, temperature, leucocyte and pneumococco-opsonic index curves heavy line, leucocytes; broken fine line, pneumococco-opsonic index. Injections of

in the left gluteal region was increased. The throat was normal. The lungs showed nothing abnormal. The apex-beat of the heart was in the fifth interspace just inside the mammillary line. There was no thrill. The left border of heart dulness extended 1 cm. to the left of the left nipple and the right border was on the right sternal edge; the upper border at the third left rib. There is a soft diastolic murmur of low pitch heard best over the aortic area and transmitted down the sternum. The pulse was water-hammer in character and there was a capillary pulsation of the fingers and of the lips. The liver was palpable, soft and normal. The spleen was palpable, firm and moderately tender. The left gluteal region was swollen, elastic and very tender. There was a distinct pulsation synchronous with the heart action. A distinct thrill was obtained on pressure over the swelling and a distinct bruit was heard on auscultation. The pulse of the popliteal arteries was equal. The blood showed 4,300,000 red cells, 70 per cent. hemoglobin and 6,900 leucocytes.

Course of Disease.—On April 30 the leucocytes were 13,600; on May 16, 14,300 and gradually increased to about 23,000 on May 25, then declined in number and on June 25 were 10,000. The hemoglobin gradually fell to 50 per cent. on June 25 and the red cells to 3,300,000 on the same date. The urine was loaded with amorphous urates; specific gravity, 1.029; it contained a trace of albumin with a few hyalin and granular casts. Toward the end of the illness a few red cells were found in the urine. On April 30 blood culture revealed the pneumococcus in pure culture; again the same result on May 5. The temperature curve was distinctly septic as shown by the chart. On May 12 a needle was introduced into the aneurismal swelling of the gluteal region and pure bright blood was obtained at the depth of 3 cm. From this blood a pure culture of the pneumococcus was obtained. On June 16 a small pulsating mass was developed under the left jaw and grew in the last few days to the size of a walnut. It was distinctly pulsating and showed a thrill on pulsation and a bruit on auscultation. On June 24 a petechial rash appeared on the skin and conjunctiva. On June 19 in the afternoon there suddenly developed a complete right-sided hemiplegia and the patient passed into coma and died.

Beginning on May 14 the patient was vaccinated with his own dead pneumococci. This was repeated on May 23, June 1 and 10. The result of these vac-



in Case 5. Solid heavy line indicates pulse; solid fine line, temperature; broken dead organisms indicated by arrows.

cinations on the clinical course, the blood and the autogenous bacteria was practically the same as in other patients. (See Chart 3.)

Case 6.—Miss E. T., aged 18, schoolgirl, was referred to my consultation room by Dr. C. M. Johnson, of Harvard, Ill.; died Sept. 1, 1908. Diagnosis: infective endocarditis, pneumococcemia and mitral insufficiency.

History.—The patient came to Chicago with her mother, after traveling for two hours on a railway. The history given was that she always had been delicate and had suffered from all of the ordinary diseases of childhood. The catamenia were established at 14 years and were of the twenty-eight-day type. From the time she was 12 to 13 years of age the patient suffered from epistaxis, which persisted until the nasopharynx was treated by a specialist. She was a student in the University of Illinois during 1907 and worked hard. During the winter of 1907-8 she suffered from an attack of acute tonsillitis and was in bed for one week. Following this illness she attended to her duties and returned to

her home in June. At that time she recognized that she was weak, had no endurance, was very nervous, had no appetite, poor sleep, dyspnea on exertion and suffered from palpitation of the heart.

Examination.—When seen on July 14, 1908, the patient was pale, general nutrition poor, general muscular weakness manifested by tremulousness. The tonsils were only moderately enlarged and were not red or visibly infected. The left border of the heart extended 11 cm. from the center of the sternum; the base to the left second rib and the right border to the right sternal edge. The apex-beat was diffuse and the heart action tumultuous. Loud systolic and diastolic murmurs were heard over the whole precordia. A very loud rough systolic murmur was heard in the mitral area transmitted to the left axilla and back. The pulmonary second tone was moderately accentuated. With the exception of a few moist râles over the bases, there was nothing abnormal to be found in the lungs. The liver was palpable at the costal edge. The spleen was palpably enlarged and not tender. The abdomen was contracted. There were no purpuric spots discernable. The blood showed 3,500,000 red cells, 50 per cent. hemoglobin, 21,000 leucocytes. A blood culture made at this time showed 6,500 colonies of the pneumococcus in pure culture from each cubic centimeter of blood. The urine showed a trace of albumin without other abnormal elements. The temperature was 101.6, the respirations 30 and the radial pulse 140 per minute.

Course of Disease.—The patient was sent to her home with a letter to the physician indicating the diagnosis and treatment. She declined steadily. Two vaccinations of the autogenous pneumococcus were made on Aug. 7, 1908, and about one week later. Following the first dose of vaccine (200,000,000 dead pneumococci) there was less fever and the patient appeared brighter for two or three days. The second vaccination produced no apparent effect. On August 26 there were three subcutaneous nodules which were small, slightly red and tender. No petechial spots appeared. The patient died Sept. 1, 1908, and no autopsy was obtained.

CASE 7.—Miss S., aged 21, student, seen with family physician, Dr. George Keenan at Madison, Wis., June 2, 1907; died in July, 1907. Autopsy. Diagnosis: chronic infective endocarditis, pneumococcemia and pulmonary vegetative valvulitis.

History.—The patient had always enjoyed good health until the beginning of the present illness, about fourteen months ago. During the latter part of the preceding year she was a student in the university and became nervous, languid, had a poor appetite and was obliged to give up her studies. During the summer vacation there was some improvement in the general condition, but no record was made of any physical examination during that time. She had not suffered from any local infectious disease like tonsillitis. During the fall of 1906 she attempted school work again but soon was obliged to give it up because of lessened strength and endurance, poor appetite, general nervousness and dyspnea on exertion. It was noticed that she was pale and there was a slight cough, especially on exertion, which was believed to be due to a cold. During that time it was noted that the temperature ranged between 99 in the morning to 102 in the evening. A tentative diagnosis of probable tuberculosis was made and the patient was sent south for the winter. There she was out of doors and made some general improvement but remained weak, had a poor appetite, shortness of breath on exertion and had more or less cough, especially after exertion or immediately after changing from a sitting to a standing position or immediately after lying down. She returned to her home in the early summer and remained up and about.

Examination.—The family physician finally was called and found an evening temperature of 103, a rapid pulse, a secondary anemia with 3,624,000 red cells, 6,500 leucocytes and 55 per cent. hemoglobin. The urine was normal. A con-

sultation was held at this time with Dr. Ogden, of Milwaukee, and resulted in the finding of a few crackling râles over the top of the right lung, palpable splenic enlargement, secondary anemia, a blowing murmur over the base of the heart with rapid heart action and much physical prostration. The temperature from that time was intermittent in character; normal or nearly so in the morning with a rise to 102 or 103 or more in the evening. (See Chart 3.) On June 2, 1907, when seen with Dr. Keenan, the general physical condition as mentioned above was noted but more particularly there was a rapid and tumultuous heart action, together with murmurs during both phases of the heart action and heard over the whole precordia. No petechial spots could be found on the skin or mucous membranes. The spleen was enlarged and somewhat tender. A few crackling râles could be heard over the bases of both lungs posteriorly. There was no consolidation. The abdomen was moderately distended; the liver palpable and moderately tender. The pelvis, examined per rectum, showed a normal condition. A specimen of blood showed a tuberculo-opsonic index of 0.7; a pneumococcus opsonic index of 0.6 and a streptococcus opsonic index of 0.7. Blood cultures were made by Dr. E. C. Rosenow, and the pneumococcus in pure culture was obtained.

Course of Disease.—Following this diagnosis the progress of the case was rather rapid and death followed early in July, 1907. In the interval between June 10 and the death of the patient she was inoculated with the autogenous dead pneumococcus in small quantities; not more than 2,500,000 to 5,000,000 of

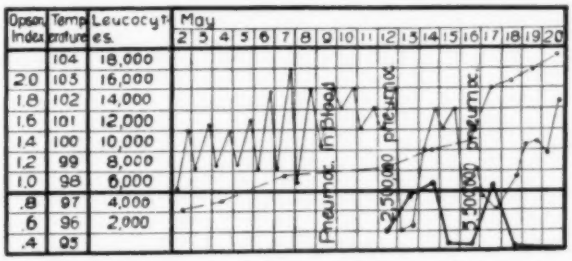


Chart 4.—Pneumococco-opsonic index, temperature and leucocyte curves in Case 7. Solid heavy line indicates pneumococco-opsonic index; solid fine line, temperature; broken fine line, leucocytes. (From the *Journal of Infectious Diseases*, Chicago.)

the bacteria were used. Following the vaccinations there was some improvement in the clinical phenomena as evinced by a lessened height of the evening temperature and the patient said that she felt better. (See Chart 4). The pulse-rate and the physical signs did not change. Four days before death a moderate pulmonary hemorrhage occurred and the patient failed rapidly and died from exhaustion. An autopsy was made.

Anatomical Diagnosis.—Vegetative and ulcerative endocarditis of the pulmonary valves and arteries; subcutaneous and renal hemorrhages; multiple old and recent pulmonary infarcts; serofibrinous pleuritis; cloudy swelling of the heart, liver and spleen; hyperplastic splenitis; anemia; passive hyperemia of liver and spleen; hydrothorax; hydroperitoneum and hydropericardium.

Postmortem Examination.—It was noticed particularly that the pulmonary valves were covered with large grayish-yellow cauliflower-like vegetations which nearly filled the lumen of the arteries at the base of which the valves were ulcerated. Some of the masses were 2 cm. long. The intima of the pulmonary arteries

just above the valve was ulcerated. At the point of the bifurcation of the pulmonary arteries there was a thrombus which was 0.75 cm. thick, solidly attached and could be followed to the left upper lobe where it ended in a softened infarct. Several small branches of the left pulmonary arteries were thrombosed. In the right lung was also an extensive thrombosis, in a branch which led to the left infarct in the lower lobe. After removal of some of the thrombi from the smaller branches the intima appeared rough and even ulcerated.

Bacteriologic Examination.—A pure culture of the *Streptococcus pyogenes* was obtained from the fluid in the peritoneum, pleural and precordial sac and from the heart's blood as well as from the spleen, liver, heart and the large infarctions. The *Staphylococcus aureus* was also found in softened infarcts. Emulsions from the vegetations on the tricuspid valve and ventricle contained both streptococci and pneumococci, of which the former were the more numerous.

Case 8.—Mrs. N. W., aged 35, first seen as ambulatory patient, Dec. 18, 1907; confined to bed at last account: Diagnosis: chronic infective endocarditis, pneumococcemia, mitral stenosis and cardiac dilatation.

History.—The patient had borne three children; she had been fairly well until a year ago before she came under observation. There was no history of rheumatic fever or any other acute infectious disorder. During the last year she had been treated for various complaints including possible pulmonary tuberculosis and because of the latter diagnosis had lived much in the open air and had attempted to exercise, even when this caused great discomfort. When first seen the patient complained of shortness of breath on exertion, general weakness, some edema of the ankles and during the day an inability to lie flat in bed or on the right side, a sense of fulness and of oppression in the chest which amounted to pain on the slightest exertion. These symptoms began a year before admission and gradually increased to the maximum at the present time.

Examination.—This showed marked pallor with cyanosis of the lips, visible mucous membranes and finger-nails. The mucous membrane of the mouth and throat was pale and there was no evidence of infection about the teeth or throat. The lungs showed a few moist and dry râles over both apices and at the bases. There was no evidence of consolidation anywhere in the lung. The left border of the heart was 15 cm. from the midsternum, the apex at the sixth interspace. There was a marked thrill at the apex. A rough presystolic murmur was heard in the mitral area and there was a very marked accentuation of the second pulmonary tone. The left auricle was much dilated. The right border of heart dulness extended 2 cm. to the right of the sternum. There was no venous pulse in the neck. The abdomen was moderately distended. The spleen was not palpable. The liver could easily be palpated and was tender to the touch.

Course of Disease.—The patient was sent to the Presbyterian Hospital, where subsequent examinations confirmed the findings made above. The urine examined on several occasions showed a trace of albumin, with a few hyalin and granular casts. The temperature for nearly two months while the patient remained in the hospital was usually normal in the morning and from 100 to 101 in the afternoon. A blood culture made on May 5, 1908, gave a pure culture of the pneumococcus. Immediately after this the patient returned to her home in Iowa, where she was under the care of a local physician who was directed to keep the patient in bed under hygienic surroundings and to attempt to improve the resistance of the patient by supporting treatment. On Sept. 19, 1908, an inquiry was made by letter and the statement came back from the husband of the patient that she was not as well, was very weak and confined to her bed with a low form of fever. The pneumococcus obtained by culture resembled that obtained from other patients suffer-

ing from a like condition. A subculture of this organism was injected into the vein of the ear of a rabbit and produced vegetative aortic endocarditis from which the animal died.

CASE 9.—Mr. E. H. B., aged 29, single, clerk, was seen in consultation with Dr. Blatchford, of Chicago, in July, 1905; died in November, 1905. Autopsy: Diagnosis: chronic infective endocarditis, streptococcemia, aortic insufficiency and mitral insufficiency.

History.—The patient had always been a vigorous, healthy man who had suffered from no important disease in his life. On April 10, 1905, he had a moderately severe attack of tonsillitis which confined him to his bed for three days. He then returned to work and appeared to be in the usual condition of health until the latter part of June, 1905. He then noticed lessened strength and endurance and was nervous and irritable. On July 24, 1905, his physician found him with a high fever and general prostration.

Examination.—On July 25 the physician found the patient's temperature 101 F., pulse 90, respiration not accelerated. The only abnormal physical finding was some swelling of the left knee-joint with moderate tenderness and no redness. The first tone in the mitral area appeared to be somewhat impure. The hemoglobin was 95 per cent., red cells 4,900,000 and leucocytes 16,000. The differential count of the leucocytes showed a normal condition. On Aug. 1, 1905, Dr. E. C. Rosenow made a blood culture and isolated an organism which appeared to be a streptococcus in pure culture. When inoculated in large doses into animals the organism appeared to be of a low grade of virulence.

Course of Disease.—On August 2 an aortic systolic murmur was heard and the left border of dulness extended 10 cm. to the left of the midsternum. On August 4 there was pain and swelling of the left ankle lasting for a few hours. On August 20 there was a slight swelling and tenderness of the right wrist. On Sept. 5, 1905, there was severe abdominal pain lasting for twelve hours, the cause of which was not clear. During August and September the leucocyte count varied between 14,000 and 25,000 with a normal proportion of the various white cell elements. During August a diastolic aortic murmur developed and later a mitral systolic murmur was heard. The temperature was of a septic type about 99 in the forenoon and varying from 100 to 104 in the evening. About every six to eight days there was usually a sudden elevation of temperature without chill which was accompanied by an increased leucocytosis. Petechial spots appeared a short time before death in the latter part of November, 1905. During the latter part of the illness there was dilatation of both sides of the heart with a loud systolic murmur, heard in the mitral area and transmitted to the left and a soft blowing diastolic murmur in the aortic area transmitted down the sternum. The spleen was palpable and tender, the liver slightly enlarged and tender, and the urine contained a trace of albumin, a few hyalin and granular casts and a few red cells. An autopsy was held.

Anatomical Diagnosis.—Acute vegetative and ulcerative endocarditis of the aortic and mitral valves with aneurism of the aortic valve and beginning dissecting aneurism of the aorta; hypertrophy and dilatation of the heart; ecchymosis of pericardium; fatty degeneration of myocardium; hydropericardium; hydrothorax; hydroperitoneum; passive congestion of liver and spleen; acute nephritis; old and recent renal infarcts with deformity of right kidney; periappendiceal adhesions.

Bacteriologic Examination.—Cultures from the heart valve showed the streptococcus alone. Cultures from the kidney were sterile. The organism found in the cultures from this patient's blood and from the vegetations on the heart valve was called the streptococcus. As stated above, it was of low virulence, for when injected into animals in large amount it did not cause death. At this time sub-

cultures of the organism were not studied by Dr. E. C. Rosenow as was done in subsequent cases. This so-called streptococcus grew in plate cultures and showed the lessened virulence of strains of organisms obtained from other patients when given in subcultures, injections of which into animals was followed by recovery and which proved to be the pneumococcus. In all probability therefore, the organism found here was the pneumococcus but is presented in this group of cases of the streptococcus. The vegetations on the valves grew in a dense mass as in other cases of pneumococcemia and endocarditis.

This patient had been repeatedly treated with injections of a commercial antistreptococcal serum without benefit.

CASE 10.—Mr. J., aged 52, lumberman, was seen with his physicians, Dr. McKechnie and Dr. J. L. Miller, of Chicago, in November, 1908; died March 4, 1909. Autopsy. Diagnosis: infective endocarditis, pneumococcemia, mitral insufficiency.

History.—The patient had been a strong and healthy man all his life. His business cares were great. He was addicted to tobacco and the overuse of alcohol. No history of venereal disease could be obtained. Off and on for several years he had suffered from various muscular ailments and disturbances of the digestive organs due to habits of life but had never presented any evidences of physical disease of importance. During the summer of 1908 the patient suffered from abscesses about the gums with pyorrhea alveolaris. This had noticeably infected the right upper second bicuspid tooth and an abscess developed also over the left upper first molar for which he received treatment from his family dentist. During the late summer of 1908 the gums and teeth were in bad condition, many of them loose. In July, 1908, the patient noticed a lessened strength and endurance; at times was chilly and when the temperature was taken on a few occasions it was found to range as high as 100. No record of the temperature was kept at this time and the feeling of ill health was supposed to be due to overwork. At this time it was noticed, too, that he had transient attacks of pain and some swelling in the various joints, especially of the feet, which appeared to be definite rheumatism. In the early part of November he was on a hunting and fishing trip and returned home in a worse condition than before his vacation. His physician found on examination no special physical disturbances except slight swelling and tenderness in the right great toe-joint. This was diagnosed as gout. The patient remained at home from this time on, with a gradual loss of strength and temperature ranging from 98 to 99 in the morning to 100 to 102.5 in the evening. In the latter part of November, 1908, a blood examination showed 11,000 leucocytes. To determine the cause of the temperature a Widal test was made at the Municipal Laboratory of Chicago and was said to be positive. The patient was then placed on typhoid orders and treated as a typhoid fever patient for two or three weeks. He then suffered from a sudden left-sided hemiplegia with a rapid rise of temperature to 106. The temperature soon dropped to the former range; the hemiplegia improved and the patient returned to much the same condition as before. The examination of the heart up to this time had been entirely negative. From this time onward a systolic murmur was heard occasionally and later became permanent. The left heart border was extended to the left and the pulmonic second tone was somewhat accentuated.

Examination.—Early in December I saw the patient with his physicians and confirmed the physical findings noted by them; that is, a septic type of temperature; a slight left hemiparesis; the patient conscious but answering questions slowly and taking but little interest in his surroundings; slight dilatation of the left heart with a mitral systolic murmur transmitted to the left and accentuation of the second pulmonic tone; the lungs negative; the liver palpable, enlarged and somewhat tender; the spleen not palpable; a few petechial spots in the skin in

various parts of the trunk and extremities. Blood cultures were made by Dr. E. C. Rosenow on December 6, 1908. The first two blood cultures were negative but a third and a fourth culture yielded the pneumococcus. Repeated Widal tests now proved to be negative. On December 13 the hemoglobin was 85 per cent., the red cells 4,000,000, the leucocytes 17,700 with a preponderance of polymorphonuclears. On February 22, 1909, hemoglobin was 70 per cent., red cells 3,200,000, leucocytes 12,000.

Course of Disease.—The patient was vaccinated with his own dead bacteria on several occasions without any manifest signs of improvement. He was also given intravenous injections of normal human serum which were followed by a marked reaction consisting in a rise of temperature, rapid heart action, etc. The details of the results of these vaccinations and of the use of human serum will be discussed in a paper by Dr. E. C. Rosenow. The patient continued in this condition until March 4, 1909, when he died from exhaustion.

Unfortunately an undertaker had embalmed the body before consent was given for an autopsy.

Autopsy.—This showed a markedly hypertrophied and dilated heart, vegetative and ulcerative endocarditis of the mitral valves, infarcts of the kidneys and spleen and fatty degeneration of the liver. Large massive vegetations were found on the mitral valve. These were grayish-red. Both anterior and posterior leaflets were involved. The growths were situated on the upper surface of the valves and extended for a distance of 2 cm. into the auricle. The free margin of the masses of vegetations were necrotic.

CASE 11.—T. W., male, single, aged 35, was admitted to the Presbyterian Hospital, Chicago, Oct. 7, 1905; died Nov. 17, 1905. Diagnosis: infective endocarditis, streptococcemia and mitral insufficiency.

Present Illness.—The patient came to the hospital complaining of pain, weakness and lassitude; shortness of breath on exertion; lessened appetite and poor sleep. He gave no history of previous illness of importance and a negative family inheritance.

Physical Examination.—This showed slight blueness of the lips and visible mucous membranes and general pallor; throat normal. Lungs showed no evidence of physical change; left border of heart dulness extends beyond the nipple line, the base to the third rib and the right border to the right edge of the sternum. A rather loud systolic murmur replaced the first sound of the heart and was transmitted to the left. The arterial walls appeared to be thickened. The abdominal organs were negative. The blood pressure taken with a Stanton instrument was 155 mm.

Course of Disease.—On October 9 a few moist râles were heard at the bases of both lungs. There was cough with slight mucopurulent sputa which was negative for tubercle bacilli. A blood culture was attempted on October 17 and was negative. The urine on admission and during October showed diminished amount for twenty-four hours with a specific gravity ranging from 1.010 to 1.020, albumin usually absent. A few hyaline and granular casts usually present and a few shadows of red cells were usually found. On October 25 a blood culture was made and a streptococcus-like organism in pure culture was obtained. On October 27 the spleen was palpable for the first time and petechial spots were noticed in the skin of the chest and abdomen. From this time onward petechial spots occurred in crops. On November 6 a second positive blood culture with the streptococcus was obtained. The urine contained at this time a few red cells and a few white cells with a trace of albumin and a few hyalin and granular casts. On November 6 a blood examination showed 3,600,000 red cells, 16,450 leucocytes and 61 per cent. hemoglobin. The temperature of the patient during the stay in the hospital was of septic type ranging in the morning about 99 and from 101 to

102 and on a few occasions as high as 103 to 103.8 in the evening. The pulse-rate was rapid, ranging from 100 to 120; respirations from 24 to 36. On November 14 the patient received 20 c.c. of antistreptococcus serum and this was repeated on November 15. There was no alteration in the clinical symptoms after the use of the serum and the patient died of exhaustion on Novmber 17. No autopsy was obtained.

The organism isolated in this case, like that in Case 9, was not studied as carefully as the organism from later cases, but it had the morphologic characteristics of the organism which later also proved to be the pneumococcus. It is, however, classed as a streptococcus infection in this series.

CASE 12.—W. P., aged 35, male, manufacturer, was seen in consultation with Dr. H. B. Favill, of Chicago, in October, 1903; died. No autopsy. Diagnosis: infective endocarditis, pneumococcemia, aortic insufficiency and mitral insufficiency.

History.—During childhood patient suffered from severe attacks of rheumatic fever in which the endocardium was involved. As a result he suffered during childhood and thereafter from a mitral insufficiency which became fully compensated and caused him no especial inconvenience excepting that with continued overexertion he suffered from a moderate dyspnea and palpitation of the heart. In the fall of 1902 the patient suffered from a low type of fever which was pronounced typhoid by the physicians in charge. The patient was confined to his bed or house for over two months and had a slow convalescence. There was doubt expressed by the physician who was in consultation at the time that this was typhoid, but in the absence of definite signs of any other disease, the patient was treated for typhoid fever. Following this attack the patient did not regain his usual strength and vigor. He appeared pale, listless and expressed himself as feeling weak and tired. He remained for a time at Hot Springs, Va., taking the baths, from which he received no benefit. During the early fall of 1903 he again was confined to his house and bed with a low form of fever which proved to be septic in character. He suffered from dyspnea especially on the least exertion, cough, rapid heart action and great nervous irritability. The heart was moderately dilated to the left and there was a loud rough systolic murmur heard in the mitral area which was transmitted to the left, and a soft blowing murmur in the aortic region transmitted down the sternum.

Course of Illness.—The spleen became palpable, the urine contained microscopic blood with a trace of albumin and a few hyalin and granular casts. Petechial spots later appeared in the skin in successive crops. When the patient was seen in consultation with his physician, Dr. Favill, a blood culture was suggested which was made and proved to be a pure culture of the pneumococcus. This was verified by subsequent cultures and by subcultures and by injections into animals. The patient died of exhaustion and no autopsy was permitted.

In the light of the termination of this case, it is not improbable that there was a low grade of infective endocarditis during the time it was diagnosed as typhoid fever and in the interval between that and the final illness there was a continuation of the heart infection which finally became so severe that the patient became bedridden.

CASE 13.—Miss F. S., aged 18, was admitted to the Presbyterian Hospital Oct. 28, 1907, on the service of Dr. B. W. Sippy, who requested me to see the patient with him and has kindly consented to a report of the patient in this series. She died Jan. 22, 1907. Autopsy. Diagnosis: Infective endocarditis, pneumococcemia, aortic and mitral insufficiency.

History.—Patient had an attack of acute rheumatic fever six years before admission which left a mitral lesion. Three months before admission to the hospital she had an attack of pain in the right side of the chest of a sharp, sticking character which was aggravated by breathing and by coughing. There was some

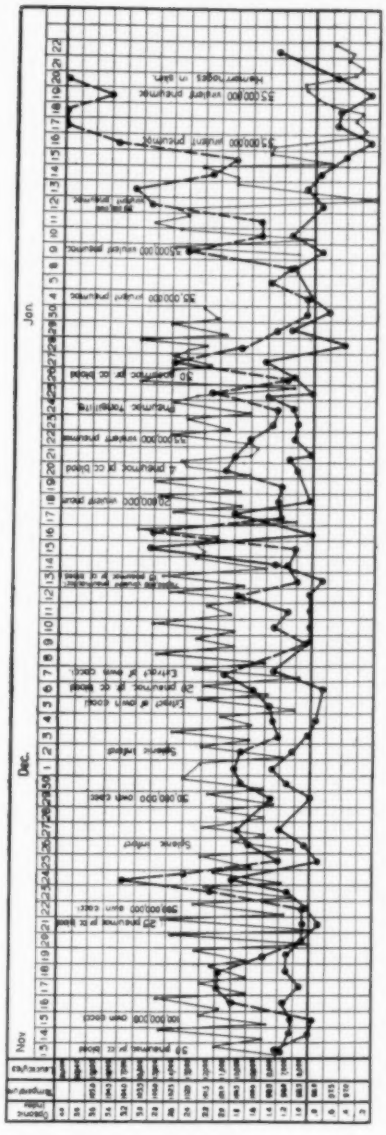


Chart 5.—Pneumococco-opsonic index, temperature and leucocyte curves in Case 13. Solid heavy line indicates pneumococco-opsonic index; solid fine line, temperature; broken heavy line, leucocytes. (From the *Journal of Infectious Diseases*, Chicago.)

fever but no cough. The patient remained in bed for a week and then got about but did not feel well and it was noted that there was usually an evening temperature varying from 100 to 101 or more. She felt weak for a long time, had a poor appetite and was nervous and irritable. Three weeks before admission the left ankle became swollen and painful. This lasted for a week. No other joint involvement occurred. On admission the patient complained of chilliness, followed by a sensation of heat, prostration and weakness. The bowels were regular, the appetite good. The patient slept fairly well.

Examination.—On admission there was a decided pallor of skin and mucous membranes. There were no petechial spots; no enlargement of the superficial lymphatic glands. The patient was fairly well nourished. There was no infection of the throat. The lungs were normal. Cardiac dulness extended to the left outside of the mammillary line. There was no evidence of dilatation of the right heart. There was a presystolic and systolic murmur in the mitral region and the systolic murmur was transmitted to the left. The pulse was rapid but regular. The spleen was not palpable.

Course of Disease.—On November 4 for the first time there was heard a diastolic murmur in the aortic area which was transmitted downward and a water-hammer pulse and capillary pulsation were noted. On November 18 the spleen was distinctly palpable. On November 25 there was pain in the left side of the chest and in the shoulder, aggravated by breathing. On December 2 the patient complained of a severe pain in the left hypochondrium and the spleen was tender. There was a secondary anemia, hemoglobin diminished to 50 per cent. and a moderate leucocytosis with a normal proportion of white cells. The coagulation time of the blood was 3.5 minutes. On December 25 the patient suffered from an acute attack of pneumococcus tonsillitis. The submaxillary glands were tender and swollen but did not suppurate. Petechial hemorrhages of the skin appeared for the first time. The pneumococcus in pure culture was obtained from the blood. From this time on the patient failed rapidly. The pneumococco-opsonic index was below the normal and the leucocytosis increased. There was a progressive secondary anemia with hemoglobin reduced to 28 per cent. The pulse remained regular until a short time before death, when the heart became dilated and irregular in action.

An autopsy was held on January 22 and revealed:

Anatomical Diagnosis.—Ulcerated mitral, aortic and mural endocarditis with characteristic vegetative growths. There were multiple infarcts of the spleen; petechial hemorrhages of the skin; anemia; fibrinous pleuritis and peritonitis; acute tracheobronchial lymphadenitis; hyperplasia of the spleen; edema of the lungs; cloudy swelling of the liver, kidneys and myocardium; hypertrophy and dilatation of the heart; obliterative fibrinous pericarditis.

Bacteriologic Examination.—From the serum, blood, peritoneal fluid, right pleural exudate and from the emulsion of the vegetation of the heart valves there were obtained Gram-positive cocci arranged in clusters and chains and in twos and from the vegetations emulsion there was obtained also a Gram-negative bacillus. Seven cultures gave a proportionately large number of pneumococci, a few *Staphylococci aurei*, and the blood yielded the *Streptococcus pyogenes* in addition. The *Bacillus mucosus* also was obtained from the vegetation emulsion.

The characteristics of the pneumococcus obtained from the blood before and after death were exactly similar to those described in the earlier part of the paper.

This patient was inoculated with the dead pneumococci of her own culture. Chart 5 shows the dates of inoculation, the dose and the result upon the temperature, the leucocytosis and the pneumococco-opsonic index.

CASE 14.—A. K., male, married, aged 30, was seen with his family physician, Dr. Frank S. Johnson, Chicago; condition practically unchanged at last account. Diagnosis; infective endocarditis, pneumococcemia, mitral insufficiency and aortic insufficiency.

History.—During childhood the patient suffered from acute rheumatic fever with a sequel of mitral insufficiency and aortic insufficiency. Compensation occurred and the patient did not suffer in consequence until his twentieth year. During his freshman year (1897-98) in college he attempted athletic work in rowing, track running, etc., with the result that during the holiday season he was confined to his bed with broken heart compensation. After a long rest compensatory hypertrophy was restored and the patient remained in fair condition of health until the early part of 1909. At this time he noticed a lessened strength and endurance, a good deal of nervousness and irritability, slight shortness of breath on exertion with some palpitation of the heart and a subfebrile temperature was noticed. He went to Hot Springs, Va., to rest and recuperate and while there became worse. Chills followed by fever occurred at irregular intervals. The spleen became palpable and he grew pale, weaker, had great dyspnea and palpitation of the heart. On the patient's return to Chicago a septic type of temperature continued, with an occasional chill, increasing weakness, palpitation, shortness of breath, etc. A secondary anemia with a low white blood count was found and his physician discovered pigmented parasite-like bodies in the red corpuscles. Antimalarial treatment was given with some amelioration of symptoms but a continuation of the febrile condition, the weakness, etc.

Examination.—When seen in consultation on May 25, 1909, the patient was found to be pale and weak; a few petechial spots were found in the skin of the back, the heart was dilated especially to the left and the heart action was rapid. A soft blowing diastolic murmur was heard in the aortic area and transmitted down the sternum, also a loud systolic murmur in the mitral area transmitted to the left with accentuation of the second pulmonic tone. The lungs were clear. The spleen was palpable; the liver not enlarged; the urine practically normal.

Immediately thereafter two blood cultures were made which were negative. On May 29 and June 10 blood cultures were made by Dr. E. C. Rosenow and a pneumococcus in pure culture was isolated both times. This organism proved to have all the characteristics of the pneumococcus isolated in other cases of infective endocarditis.

The patient died in July. Autopsy revealed vegetative growths on aortic and mitral valves; aortic and mitral insufficiency; infarcts of spleen and kidneys, etc.

100 State Street.

A NOTE ON THE VENOUS PULSE IN PAROXYSMAL TACHYCARDIA

FRANCIS W. PEABODY, M.D.
BALTIMORE

While paroxysmal tachycardia is a clinically well-recognized symptom-complex, its exact pathology is not as yet by any means understood. The introduction of graphic methods in the study of cardiac phenomena has already resulted in some light being thrown on this condition, and it is only through such means that its ultimate explanation may be looked for. Since, however, the number of cases in the literature of which good venous tracings have been taken is decidedly limited, it has seemed worth while to report two instances in which records of the jugular pulse were obtained.

In general it may be said that from the point of view of the venous pulse all cases of paroxysmal tachycardia apparently fall into one of two groups (Hirschfelder,[1] Schmoll[2]). The first includes those cases in which the venous pulse is of the normal or "auricular" type. In the second class the venous pulse assumes the "ventricular" or "positive" type, and there is no evidence of any contraction of the auricles. Cases of the first class have been reported by Schmoll[2] and by Cowan, McDonald and Binning.[3] Cases in which the venous pulse is "ventricular" have been described by Schmoll,[2] Rihl,[4] Hay,[5] Hirschfelder[6] and Mackenzie.[7] In a discussion of this subject it is of the utmost importance, as Hirschfelder[1] has pointed out, to distinguish between cases of idiopathic paroxysmal tachycardia, with sudden onset and cessation, and cases of simple rapid heart action beginning and ending more or less gradually.

---

1. Hirschfelder: Contributions to the study of auricular fibrillation, paroxysmal tachycardia, and the so-called auriculo-(atrio)-ventricular extrasystoles. Johns Hopkins Hosp. Bull., 1908, xix, 322.
2. Schmoll: Paroxysmal tachycardia. Am. Jour. Med. Sc., 1907, cxxxiv, 662.
3. Cowan, McDonald and Binning: The venous pulse in paroxysmal tachycardia. Quart. Jour. Med., 1909, ii, 146.
4. Rihl: Atrioventrikuläre Tachycardie beim Menschen. Deutsch. med. Wchnschr., 1907, xxxiii, 632.
5. Hay: Paroxysmal tachycardia. Edinburgh Med. Jour., 1907, xxi, 40.
6. Hirschfelder: Observations on paroxysmal tachycardia. Johns Hopkins Hosp. Bull., 1906, xvii, 337.
7. Mackenzie: Diseases of the heart. London, 1908.

The following cases were observed in the wards of the Johns Hopkins Hospital, and I am indebted to Dr. Barker and Dr. Thayer for permission to report them:

CASE 1.—M. M., female, general number 67,343, medical number 23,725, married, aged 33, admitted Feb. 16, 1909, discharged March 9, 1909, complains of "fluttering round heart, and pain in chest and back."

History.—Family history good. She has been married seventeen years and has had seven children. Had diphtheria when a child, but recovered without complications. Seven years ago she had typhoid fever; "chills and fever" three times in the last three years. Two months ago she had pneumonia. Otherwise she has always been well. Average weight 115 pounds.

Present Illness.—For some months she has suffered from "aching in bones," "extreme weariness," and shortness of breath on slight exertion. Occasionally she has had some slight "fluttering around heart." Two weeks ago all her symptoms

Fig. 1.—Paroxysmal tachycardia, Case 1; pulse rate, 215. In all tracings, timer marks tenths of seconds; lowest tracing is from the brachial artery, the second from the carotid artery, and the third from the jugular vein.

became worse, and eight days ago she had an attack of "fluttering" which lasted for nine hours. Similar attacks lasting for longer or shorter periods have recurred every day since. She has been in bed for a week, and during this time has had drenching sweats every night. She has been nursing her baby and her breasts are still lactating. Hemoglobin, 75 per cent.; red cells, 4,000,000; white cells, 10,600.

Physical Examination.—This shows a poorly nourished, very pale woman. There are no physical signs of importance except in the heart. The apex impulse is felt in the fourth space, 7 cm. to the left of the mid-sternal line. The relative cardiac dulness extends 10 cm. to the left in the fourth space, above to the upper border of the third rib, and to the right 3 cm. from the mid-sternum. The rate is 200 to the minute. There is no arrhythmia. No murmurs can be distinguished except for a "short, high-pitched, apparently systolic murmur," which is localized in the tricuspid area. The lungs are clear. The liver flatness extends from the

sixth rib to 3 cm. below the costal margin in the right mammary line, the edge doubtfully palpable. The radial pulse is extremely weak, scarcely more than a flutter. No pitting over ankles.

Course of Disease.—February 17: This morning the pulse rate is 90, and the loud systolic blow, maximum over the tricuspid area, has disappeared.

February 18: At 5:30 p. m. the patient complained of "fluttering of the heart," and the heart's rate, taken at the apex, was found to have risen from 90 to 200. At about 8 p. m. tracings of the venous pulse were taken (Fig. 1). Pressure was then made over the vagus nerve in the neck, and the rate dropped suddenly from 200 to 116 (Fig. 2). The patient was much relieved and said she felt as if she would go to sleep.

On the following morning the pulse rate was 100.

On the day after admission there was a trace of albumin in the urine, but the examinations have otherwise been negative. The blood pressure has ranged from 76 to 102 mm.

After the attack of tachycardia, which was stopped by pressure on the vagus, she remained free from attacks until her discharge from the hospital on March 9. During this time the pulse rate ranged from 80 to 126, being generally about 100.

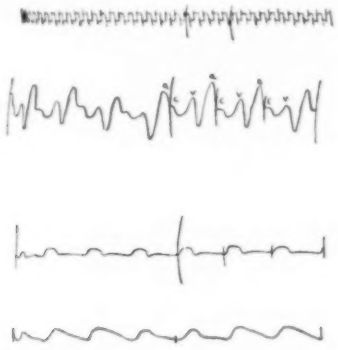


Fig. 2.—Normal rhythm after pressure on vagus nerve in neck, Case 1; pulse rate, 120.

Tracings from the jugular vein, the carotid and brachial arteries were taken from this case during the attack and immediately after the attack was stopped by pressure on the vagus. The venous pulse during the attack shows only two waves—one beginning about 0.02-0.05 seconds before the rise on the carotid pulse—obviously the *c* wave— and a second, less marked wave following. The latter is probably the *v* wave. The onset of this second wave occurs on an average 0.11 seconds before the next *c* wave, and it is, of course, possible that this might represent an *a* wave of auricular contraction. If it were an *a*, however, one would expect a larger wave, as it falls during ventricular systole. Moreover, it would be unusual to have so large a depression between *a* and *c* waves. The beginning of the *v* wave occurs 0.179 seconds after the *c* wave at

the normal rate, and at the rapid rate 0.160 seconds after the *c*. The relations of the crest of this second wave at the rapid rate, and of the *v* wave at the normal rate, to the dicrotic notch on the carotid artery are the same—both falling 0.03 seconds after the notch. The most probable explanation of the curve, therefore, is that it is a "ventricular" venous pulse. The tracing taken after the attack was stopped shows the resumption of the normal, "auricular" venous pulse with a well-marked *a* wave, a *c* wave, and a *v* wave. The conduction time—the a-c interval—is in this case from 0.16 to 0.19 seconds.

CASE 2.—Male, single, aged 29, general number 67,086, medical number 23,646, admitted during an attack of paroxysmal tachycardia.

History.—Family history good. Patient had scarlet fever at 14; acute articular rheumatism at 16. This was not followed by any apparent complication until he began to have shortness of breath, and on examination a mitral stenosis was discovered five years ago. For some time he has had attacks of palpitation of the heart in which the rate jumps from about 86 up to 180 per minute. These attacks of tachycardia occurred at first at intervals of about a month, but they have been much more frequent of late. Sometimes he has several in a week. The duration has varied from thirty seconds to twenty-seven hours. In the longer attacks he sometimes has cough and foamy or bloody expectoration, especially if he lies on his back. The attacks often begin without any obvious cause, but may follow a quick or sudden movement. During them he feels rather weak, and is troubled by the forcible "thumping" of his heart, but except in the longer attacks he is never forced to go to bed. Many of the attacks he is able to stop by pressure on the vagus in the neck, by vomiting, by tickling the back of the throat with his finger, or by deep inspiration. Putting the finger down the throat or inducing vomiting are fairly reliable methods of aborting the attacks. More severe attacks cease only after pressure on the vagus lasting several minutes. Some of them, however, do not yield to any method which has been employed. The longest attack—twenty-seven hours—stopped an hour and forty minutes after the intravenous injection of 1 mg. of strophanthin. It is, of course, doubtful whether the drug was a factor in its cessation. One attack stopped about three minutes after a similar injection of strophanthin, but as another began in a few hours, during the period over which the drug should still be active, there is no reason to suppose that the strophanthin itself had any effect. A variety of other drugs produce no results. During the attacks the pulse rate is usually about 180-190, and between attacks it is about 87. It is worthy of note that an *x*-ray examination has shown an osteoarthritis of the cervical spine.

Physical Examination of the Heart.—While the heart's rate is 72, the apex impulse is in the fifth space, 8.5 cm. from the median line. The relative cardiac dulness extends from 3.8 cm. to the right in the fourth space, to 9 cm. to the left of the median line in the fifth space. The first sound is well heard 20 cm. from the chest without the aid of a stethoscope. On auscultation it is sharp and snapping, and there is a characteristic presystolic murmur which begins with a *bruit de rappel* very soon after the second sound. The murmur is not audible in the axilla where the *bruit de rappel* is heard with great intensity. The accentuation of the pulmonic second is not great. The lungs are clear. The liver is not enlarged. Blood pressure, 80-90.

Diagnosis.—The case is thus one of mitral stenosis associated with attacks of paroxysmal tachycardia. On some examinations a very faint diastolic murmur of aortic regurgitation has been heard, and at times a soft systolic murmur has been

noted at the apex. The possibility of the cervical osteoarthritis being a factor in the cause of the paroxysmal tachycardia by acting on the vagus nerve cannot be excluded.

Tracings have been taken from the jugular vein, the carotid and brachial arteries during two of his attacks. Figure 3 shows the type of curve which was obtained on both occasions. The venous pulse is of the same form as that in Case 1. There are two waves, one beginning 0.018 to 0.025 seconds before the carotid rise, obviously the *c* wave, and a second which follows it. This second wave begins on an average 0.15 seconds before the *c* wave. Its onset is 0.156 seconds after the *c* wave, while the *v* wave at the normal rate begins 0.24 seconds after the *c* wave. The crest of the second wave falls 0.060 seconds after the dicrotic notch on the carotid, approximately the same time relation as that of the *v* at the normal rate, which falls 0.056 seconds after the di-

Fig. 3.—Paroxysmal tachycardia, Case 2; "ventricular" venous pulse; pulse rate, 193.

crotic notch. It is impossible to prove that this is not the wave of auricular contraction, but, as in the other case, it seems much more probable that it is a *v* wave, and that we have here also a "ventricular" venous pulse. If one should assume that this is an *a* wave, then the a-c time—the time of transmission of the impulse from auricle to ventricle—when the heart's rate is 193, is 0.15 seconds, while between attacks, at a time when the pulse rate was only 73, the *a-c* time averaged 0.17 seconds. Figure 4 is a tracing taken when the heart's action was slow and shows a normal "auricular" venous pulse with *a, c* and *v* waves. Both of these cases, therefore, seem to belong to that class in which the normal sequence of auricular and then ventricular contraction is replaced during

the paroxysms of tachycardia by a condition in which all evidence of contraction of the auricle is lost, and in which the venous pulse only shows a wave due to contraction of the ventricle. The cause of this absence of a contraction on the part of the auricle has not, as yet, been satisfactorily determined. There are, however, various conceptions which seek to explain the conditions in paroxysmal tachycardia.

Hoffmann[8] was struck by the fact that in attacks of paroxysmal tachycardia the normal rate of the heart is approximately doubled or quadrupled. As an explanation of this fact he assumed that at a point above the auricles—in the veins—stimulus-formation went on at a more rapid rate than that to which the heart could respond. Owing to diminished irritability, contractability, and conductivity—a sino-auricular

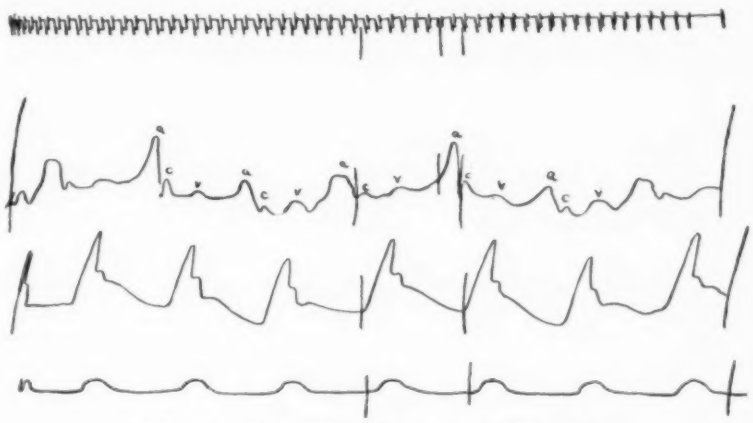


Fig. 4.—Normal venous pulse, Case 2; pulse rate, 73.

block—the auricles respond normally to only every second or every fourth stimulus arising in the veins. During the attacks there is a letting up of the normal sino-auricular block, the heart is enabled to follow the rhythm of the veins, and its rate is increased two or fourfold. While such a mechanism is an ingenious explanation of those cases of paroxysmal tachycardia in which there is a simple relation between the rates and during the attacks—although by no means all cases are of this type—there is very little experimental evidence in favor of such a theory.

According to Mackenzie,[7] in paroxysmal tachycardia the normal sequence of the heart's action is replaced by what he terms the "nodal

8. Hoffman: Verdoppelung der Herzfrequenz. Ztschr. f. klin. Med., 1904, liii, 206.

rhythm," in which the stimulus to contraction no longer begins at the venous sinus and passes to the auricle and then to the ventricle, but in which the stimulus originates in the "auriculoventricular node" of Tawara and causes a simultaneous contraction of auricles and ventricles —extrasystoles with shortened conduction time. This is the same type of ventricular rhythm which Mackenzie has described as occurring in the "absolutely irregular heart." While, however, the nodal rhythm usually gives rise to markedly irregular heart action, nodal extrasystoles may be produced in groups in which the rate is very rapid and the rhythm regular. The essential characteristic of the venous pulse in "nodal rhythm" is the absence of any wave due to auricular systole and the presence of a "ventricular venous pulse." In two of the cases reported by Mackenzie, postmortem examinations showed that the auriculoventricular bundle was pathologically affected. In one case there was infiltration by plasma cells, while in the other case the artery supplying the bundle was obliterated and there was probably disease of the bundle itself. These two instances "afford support for the view that the auriculoventricular node or bundle, by the invasion of the diseased processes, is rendered more irritable than the sinus remains, and on account of the excessive irritability starts the rhythm of the heart." Mackenzie goes so far as to affirm that the term "paroxysmal tachycardia" should be used only to cover those cases in which the "nodal rhythm" is present. Those cases of tachycardia in which ventricular contractions follow auricular contractions, as normally, he refers to as "attacks of palpitation." In the latter, he states, the rate rarely rises above 170. Mackenzie gives venous tracings from seven cases which showed "transient nodal rhythm" or typical attacks of paroxysmal tachycardia.

Rihl also has reported a case in which there were sudden changes of heart rate associated with changes in the venous pulse. When the heart was slow the venous pulse was of the normal character, but during the rapid phases only one wave was present—a wave occurring synchronously with the cubital pulse, after the ventricular contraction, and apparently due to the contraction of the auricle. Rihl concluded that during the periods of tachycardia the stimulus to contraction arose in the auriculoventricular region.

On the basis of experimental evidence Hirschfelder[1] has suggested that the cause of those cases of paroxysmal tachycardia which are characterized by the ventricular type of venous pulse is fibrillation of the auricles. By means of strong faradic stimulation applied to the auricle of a dog's heart he was able to produce auricular fibrillation, together with a sudden increase in the ventricular rate to approximately double

the normal. Both conditions outlasted the period of faradization, and in some cases were stopped by stimulation of the vagus. While it is, of course, impossible to prove that in paroxysmal tachycardia in man the auricles are in a state of fibrillation, such an explanation would account for the absence of evidence of auricular contraction, together with the sudden increase in ventricular rate which is seen in most cases, and the experimental evidence makes the work peculiarly suggestive.

Cushny and Edmunds[9] have also observed auricular fibrillation in dogs, and have suggested that the condition may be the cause of paroxysmal arrhythmia in man. In their cases the fibrillation was seen immediately after opening the chest, and was apparently due to a reflex from the sensory stimuli produced by the operation. The two theories of Mackenzie and of Hirschfelder are, however, not necessarily opposed to one another. The essential point in Mackenzie's theory is that the waves on the venous pulse in paroxysmal tachycardia represent extra systoles with shortened conduction time arising in the atrio-ventricular nodes. It is of importance, first, that Retzer[10] has shown clearly that the node of Tawara can not be found in either the embryonic or adult human heart. Second, Hirschfelder has demonstrated experimentally "that extrasystoles with shortened conduction time may arise as a result of stimuli applied directly to the auricles, and need not necessarily indicate the presence of an irritative lesion within the bundle of His or even within the system of Purkinje fibers." Thus it is quite possible that the contractions of the heart in paroxysmal tachycardia are extrasystoles with shortened contraction time, the original stimulus to which arises in an auricle which is unduly irritable or which has passed into fibrillation.

The tracings which were obtained from the cases reported here might well be explained on the basis either of Mackenzie's or of Hirschfelder's theories. On the one hand, the "ventricular" venous pulse might be due to the rapid formation of stimuli in the auriculoventricular bundle, causing both chambers of the heart to contract simultaneously, with the result that only one wave is seen on the venous pulse. On the other hand, there might be fibrillation of the auricles, so that no auricular wave is registered, in which case the wave on the venous pulse is due to ventricular contraction alone.

I am greatly indebted to Dr. W. S. Thayer and Dr. A. D. Hirschfelder for their kind assistance.

9. Cushny and Edmunds: Paroxysmal irregularity of the heart and auricular fibrillation. Am. Jour. Med. Sc., 1907, cxxxiii, 66.

10. Retzer: Some results of recent investigations on the mammalian heart. Anat. Rec., 1908, ii, 149.

RELATION OF IODIN TO THE STRUCTURE OF HUMAN THYROIDS

RELATION OF IODIN AND HISTOLOGIC STRUCTURE TO DISEASES IN GENERAL; TO EXOPHTHALMIC GOITER; TO CRETINISM AND MYXEDEMA*

DAVID MARINE, M.D., AND C. H. LENHART, M.D.
CLEVELAND, OHIO

INTRODUCTION

Throughout the course of our studies on the formation of goiter it has been our aim to collect all the data possible as to the incidence, kinds and nature of the thyroid changes in animals so that when human thyroid changes were taken up at least some fundamental conclusions could be available as a point of departure. Nevertheless, while the supplanting of indirect and accidental observations on man by the direct observations on animals is the modern and logical way of approaching a medical problem, proper regard must always be had for the difference arising out of the different positions of the different animals in the biological scale of animal life, even though evidence is fast accumulating that their pathology is quite as applicable to man as their physiology, considering their position in the biological scale. This method of approach is particularly desirable in the case of the thyroid, since the advance of our knowledge of thyroid diseases has been restricted by attempting to use human material as a basis of study. This is due (apart from the indirect and accidental nature of such observations) to the fact that complicating factors are so common and modifying conditions so frequent that pure types are not encountered with sufficient frequency in the experience of any one observer to enable him to emphasize their importance.

In the present work we first attempted to use human material, but were forced to turn back and study series of dog, sheep, pig and ox thyroids in order to find basic types of anatomical changes. Therefore, the observations on human thyroid changes are compared with similar changes occurring in the above-mentioned animals. The results of these comparisons have shown a surprising uniformity both in the iodin content and in the histological structure for all these animals—man, dog, sheep, ox and pig.

---

* From the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University.

ANATOMICAL CLASSIFICATION

The confusion that at present exists throughout all phases of thyroid changes can be inferred from the vast literature that has arisen around one phase—namely, exophthalmic goiter—in the endeavor to establish the fact that in every true case of this disease there occurs active hyperplasia of the thyroid. And, even in this single phase, there are still widely different opinions. All the other phases of thyroid changes are more or less indefinite.

Virchow[1] fully recognized the confusion existing at that time and the errors to which it was leading when he wrote: "With reference to true goiter the opinion has long been held that it comprises a series of definite species (struma lymphatica, cystica, ossea, vasculosa, etc.) which develop independently of each other. This is wrong. All these so-called varieties are none other than different modes of development of essentially the same form of goiter. They mean only different forms of terminal conditions or metamorphoses which can be combined with one another in the same tumor, and a very large and striking variety of these metamorphoses may exist in the same tumor."

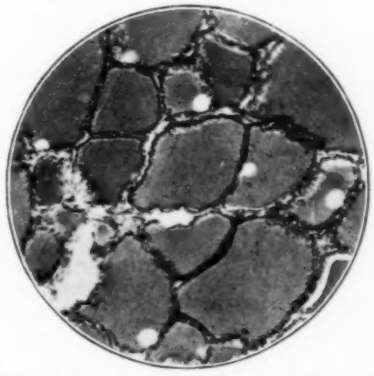


Fig. 1.—Normal thyroid (human). From a male, white subject, aged 40, dead of aortic stenosis. Iodin per gram of dried thyroid in milligrams—2,861. The sections represented in these illustrations were taken from the routine files of our human material. This material was hardened in 4 per cent. formalin. The sections were cut in celloidin and stained with hematoxylin and eosin. The magnification is the same in all, viz., Leitz, ocular IV, objective III = 95 diameters. Figures 1 to 4 represent the "Normal" or "Primary" series of hyperplasias.

Since Virchow wrote these words the advent of operative removal of goiters and the extensive reports based on this highly complicated material have in general tended to complicate the classification further.

1. Virchow. Die krankhaften Geschwülste, 1863, iii, 4.

Two major causes have assisted in this confusion. First, as Virchow pointed out, the secondary or complicating changes have been raised to the importance of the primary changes—for example, such terms as "fibrous," "cystic" or "hemorrhagic" goiter have been placed on the same plane with parenchymatous (actively hyperplastic) goiter. Second, in the correlation of the clinical phenomena with the anatomical changes and the development of the clinical-pathological classification the fact has not always been borne in mind that very great anatomical changes may occur in a short space of time and that the clinical phenomena do not necessarily change to the same extent; as, for example, the typical active thyroid hyperplasia of exophthalmic goiter may revert to a pure colloid condition within a month and the clinical picture remain that of a well-defined case of exophthalmic goiter. We have repeatedly observed this change.

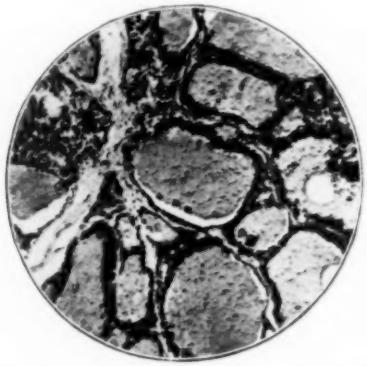


Fig. 2.—Early glandular hyperplasia. From a male, white, healthy subject, aged 30, dead of fracture of the skull, from an accidental fall. Iodin per gram of dried thyroid in milligrams = 0.877.

In the lower animals where these various secondary or complicating factors are reduced to a minimum it is quite easy to convince oneself by examining any large series of glands that there are fundamental types of thyroid changes concerned in the production of true goiter. These fundamental types are (1) the normal thyroid, (2) the actively hyperplastic thyroid (all degrees) and (3) the colloid thyroid.

With these fundamental types established, the problem of bringing the human thyroid changes into relationship with them is not difficult, although there remains in any large series of human thyroids and, to a lesser extent, of dogs' thyroids, a considerable group of glands in which the anatomical changes are so extensive and complicated as to bear little

resemblance to the primary types. This is especially true of the human operative material, in which uncomplicated forms are seen only in the active hyperplasias of childhood, puberty, pregnancy and exophthalmic goiter or in the colloid glands resulting immediately therefrom.

From an anatomical material consisting of 370 human, 850 dog, 70 sheep, 67 ox and 26 pig thyroids which we have personally collected and examined, together with a fair review of the literature, the following general schema of anatomical changes has been deduced:

I. Normal Thyroid.
II. Active Hyperplasias.
  1. Prenatal—may terminate in:
    (a) Fibrosis-atrophy.
    (b) Colloid.
  2. Childhood—may terminate in:
    (a) Fibrosis-atrophy.
    (b) Colloid.
  3. Puberty—may terminate in:
    (a) Exophthalmic goiter, fibrosis-atrophy.
    (b) Colloid.
  4. Pregnancy—may terminate in:
    (a) Exophthalmic goiter, fibrosis-atrophy.
    (b) Colloid.
  5. Exophthalmic goiter—may terminate in:
    (a) Fibrosis-atrophy.
    (b) Colloid.
III. Colloid glands.
  1. Active hyperplasia.
    (a) Simple hyperplasia—may terminate in:
      (i) Exophthalmic goiter.
      (ii) Colloid.
    (b) Exophthalmic goiter—may terminate in:
      (i) Fibrosis-atrophy.
      (ii) Colloid.
    (c) Colloid.
IV. Atrophies.
  1. Infantile.
  2. Supervening in exophthalmic goiter, tuberculosis, obesity (Dercum's disease?), etc.
  3. Physiological (old age).
V. Regeneration (hyperplasia).
VI. Degeneration.
  1. Hyaline.
  2. Calcareous.
  3. Amyloid, etc.
VII. Inflammations.
VIII. Tumors.
  1. Benign.
    (a) Fetal adenoma.
    (b) Simple adenoma.
  2. Malignant.
    (a) Carcinoma.
      (i) Originating from fetal adenoma.
      (ii) Glandular carcinoma.

(b) Sarcoma.
(c) Endothelioma, etc.

IX. Complications.
1. Hemorrhage and its sequelæ.
2. Cysts, etc.

This general outline or skeleton of the major types of changes occurring in the thyroid differs somewhat from the usual ones of text-books in several important particulars. First and most important perhaps is that colloid glands have been removed from the group of degenerations and placed on the same plane with normal glands and the hyperplasias. This was the result of both an anatomical and experimental study.[2]

Second, it indicates the sequence of changes occurring in the gland, e. g., colloid glands are placed after the active hyperplasias because it has

Fig. 3.—Moderate glandular hyperplasia. From a male, white subject, aged 31, dead of typhoid fever with intestinal perforation. Iodin per gram of dried thyroid in milligrams = 0.615.

been shown that all colloid glands have at one or more times been in the stage of active hyperplasia.

Likewise atrophies, apart from the physiological (senile) form, are in all probability always preceded by a greater or lesser degree of active hyperplasia.[3]

In the present communication we are concerned only with normal actively hyperplastic and colloid glands, inasmuch as these are the only fundamental types concerned in the production of true goiter. Certain relations with the remaining groups of the general schema will, however, be pointed out in their proper places.

2. Von Bruns: Beitr. z. klin. Chir., 1896, xvi, 521. Marine and Lenhart: Johns Hopkins Hosp. Bull., 1909, xx, 131.

3. Ord, W. M.: Brit. Med. Jour., 1898, ii, 1473. Howard, C. P.: Myxedema. Jour. Am. Med. Assn., 1907, xlviii, 1325.

The anatomical descriptions to follow will, in the main, be confined to the human thyroid, inasmuch as extended descriptions of similar changes in other animals have already appeared.[4]

I. NORMAL THYROID*

The normal human thyroid[5] differs histologically in no essential way from similar glands in the dog, sheep, ox, pig or horse. In the past histologists have differed somewhat as to the characteristics of normal glands, but these differences were dependent largely on the regional and accidental circumstances of the material used. The more recent descriptions given by Müller,[6] Bozzi,[7] and Ebner[8] show a general agreement. From these authors' descriptions, however, it can be seen that no sharply

Fig. 4.—Marked glandular hyperplasia. From a case of exophthalmic goiter in a female subject, aged 22, dead following operation. Iodin per gram of dried thyroid in milligrams = 0.292.

cut, terse description of the histology is universally accepted. This is to be expected in regard to a gland like the thyroid, which reacts so quickly

* See Figure 1.

4. Marine: Cleveland Med. Jour., 1907, vi, 45. Marine: Johns Hopkins Hosp. Bull., 1907, xviii, 359. Marine and Williams: The relation of iodin to the structure of the thyroid gland. THE ARCHIVES INT. MED., 1908, i, 349.

5. The parathyroid glands have been examined in all autopsy specimens and it may be stated that we have found them remarkably constant in number and position when one considers their normal number (four) and their size. They usually partake of the color of the thyroid, i. e., are pale yellow in the lighter red and brown yellow in the darker red thyroids. We have seen no evidence suggesting that they react anatomically with the thyroid in its goitrous changes and we believe that they are quite independent structures.

6. Müller, L. R.: Beitr. z. path. Anat. u. allg. Path., 1896, xix, 127.

7. Bozzi: Beitr. z. path. Anat. u allg. Path., 1895, xviii, 125.

8. Ebner: Koelliker's Handbuch der Gewebelehre des Menschen. Leipzig. 1899, iii, 316.

to the many changes and alterations in the body metabolism. It was pointed out by Hale White[9] that if one examined any large series of human thyroids he would find great variations in the histological appearance in subjects that, during life, showed no manifestations of diseases known to be associated with thyroid changes. This observation has been confirmed by all subsequent observers.

The perfectly normal, adult thyroid weighs between 20 and 30 gm. This is lower than the weight usually stated (30 to 40) and applies to the seacoast type, for there is no doubt that in goitrous districts much larger glands are considered normal, although from our observations we believe that all such glands have at one time or another shown hypertrophic changes, and if histologic examination shows any evidence to that effect we class them as colloid glands.

Fig. 5.—Colloid-early glandular hyperplasia. From a female, aged 21, dead of eclampsia with Cesarean section. Iodin per gram of dried thyroid in milligrams = 0.815. Figures 5 to 7 represent the "Colloid" or "Secondary" series of hyperplasias. (When this paper was sent to the publishers we had not obtained an uncomplicated specimen of colloid marked glandular hyperplasia.

The lateral lobes are in general symmetrical and of uniform size, though slight variations are not infrequent. So also with the isthmus and pyramidal portion. The outer fibrous areolar capsule is thin and strips easily, leaving a slightly lobulated smooth surface. The capsule proper is thin and translucent, and thickened portions (trabeculæ) extend into the gland, mark out the lobules, and support the blood and lymph vessels. The general color varies from a pale amber red to a bright amber red. On section the follicles can just be distinguished with the naked eye and vary greatly in diameter (0.3 to 0.5 mm.). They are filled with a clear amber-yellow viscid colloid.

9. White, Hale: Med. Chir. Tr., 1888, lxxi, 181.

Microscopically the follicles are in general round or oval closed spaces of somewhat irregular size. They are lined with a single layer of flat cubical or, at most, cubical epithelium (high cubical or columnar types of epithelium always indicate hypertrophy). The cells are quite regular in size and in certain specimens the so-called "chief" and "colloid" cells described by Langendorf[10] can be made out. These changes probably represent different secretory activities of the cells. The nuclei are small, basal, darkly staining and vesicular. The colloid lies in contact with the free border of the epithelial cells. It is homogeneous and stains deeply with eosin. The colloid of adjacent follicles may not stain with the same intensity, and colloid-like material is frequently to be seen in the lymphatic spaces—an observation usually taken as evidence that the lymphatics form the normal paths of exit for the colloid.[11] The

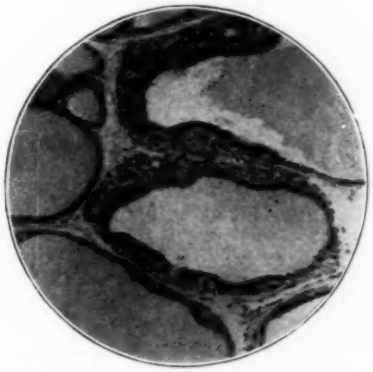


Fig. 6.—Colloid-moderate glandular hyperplasia. From a male, white subject, aged 22; clinical diagnosis: exophthalmic goiter. Patient operated on; recovered. Iodin per gram of dried thyroid in milligrams = 0.366.

blood and lymph vessels, though forming rich networks about the follicles, are not prominent, nor are the larger vessels of the trabeculæ and capsule thick-walled and tortuous as in the colloid goiters.

II. ACTIVE THYROID HYPERPLASIAS*

There is no essential difference between the forms seen in human and those seen in dog, sheep, ox or pig thyroids. Pure types of hyperplasia are, of course, less frequently observed in man. Detailed descrip-

10. Langendorf: Biol. Centralb., 1889-90, ix, 426.

11. Baber: Quart. Jour. Micr. Sc., 1877, new series, xvii, 204. Hürthle: Arch. f. d. ges. Physiol. (Pflüger's), 1894, lvi, 1. Zeiss: Inaug. Diss. Strassburg, 1877.

* See Figures 2, 3, 4, 5, 6.

tions of these changes in the dog, sheep and ox have already appeared and it remains only to outline those occurring in the human thyroid. Active hyperplasias, being the first or primary phase of goiter formation, are most frequently observed in the goiter-developing epochs—namely, childhood, puberty and pregnancy—although a great many thyroids show active hyperplasia when there is no clinical evidence of thyroid abnormality. The classical and perhaps best known example of thyroid hyperplasia in man occurs in exophthalmic goiter.

In man, just as in the lower animals, one observes all degrees of hyperplasia, from the very slightest changes from normal or colloid glands (hypertrophy) to the most marked epithelial proliferation (hyperplasia).

As has been discussed at some length in other publications (Marine and Williams[4] and Marine and Lenhart[2]), it is necessary to recognize

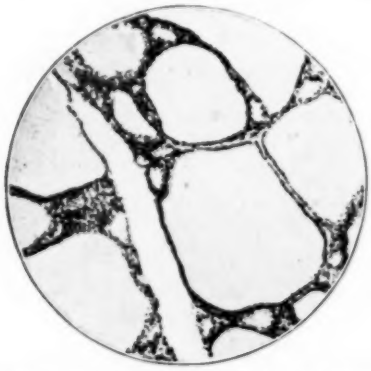


Fig. 7.—Colloid goiter. From a female subject, aged 19; case clinically diagnosed as severe exophthalmic goiter; patient had been treated for past six months by the internal administration of iodin; operated on, recovered. Iodin per gram of dried thyroid in milligrams = 4.614.

two series of hyperplasias—(1) normal (2), colloid. The normal series includes all cases of hyperplasia which are engrafted on normal glands and the colloid series of hyperplasias include all cases in which the hyperplasias are engrafted on colloid glands. This secondary hyperplasia (secondary in the sense that it is not the first time these glands have undergone active hyperplasia) is well recognized in human goiter, especially as the so-called "secondary exophthalmic goiter," and of late we have recognized that secondary hyperplasia occurs in colloid glands just as readily as primary hyperplasia occurs in normal glands, and as a result of the same causes, either with or without (usually without) the clinical signs of exophthalmic goiter. Since the conditions favorable to

the development of colloid glands (variations in food, body nutrition, locality, etc.) more commonly affect man and dog, colloid glands and the several degrees of the colloid series of hyperplasias are more often seen in these animals.

For convenience of description and of analysis we have divided the two series (normal and colloid) into subgroups, as follows: (1) *Normal-early, early, early-moderate, moderate, moderate-marked* and *marked glandular hyperplasia;* (2) *colloid-early, colloid-early-moderate, colloid-moderate, colloid-moderate-marked* and *colloid-marked.*

The early stages of hyperplasia are the most important, for the reason that the first change from the normal gland marks the first step in the formation of goiter, and it is now generally recognized that the primary phase of all true goiters is active hyperplasia (Virchow[1]).

Tracing the process of hyperplasia, the first change noted in the thyroid is an increased blood supply to the gland. The capsular vessels are dilated. They become tortuous. The capillaries surrounding the follicles are dilated and congested. The gland becomes larger and softer and takes on a brighter red color. Microscopically there is lessening of the stainable colloid; at first but palely staining, later vacuolization, and finally actual disappearance of the true colloid—its place being taken by a glandular albuminous débris in which are seen leucocytes and shed epithelial cells.

The flat-cubical or cubical epithelial cells of the normal or colloid glands at first become high cubical with larger and more vesicular nuclei; later they become columnar, and finally high columnar. Then, as hyperplasia takes place, infoldings and plications of the lining epithelium are formed. This process is apparently an attempt to increase the epithelial surface without undue general glandular enlargement. The connective-tissue framework of the capsule and trabeculæ increases. This is at first probably only a compensatory process to support the great increase of epithelial elements and the increased blood supply.

The now well-recognized and clear descriptions of the essential histological changes in exophthalmic goiter, which have been developed by Bramwell,[12] Greenfield,[13] Edmunds,[14] Farner,[15] Von Hansemann,[16] Hirschlaff,[17] Mac Callum,[18] Ewing,[19] Lewis,[20] Wilson,[21] and others, repre-

12. Bramwell: Atlas of Clinical Medicine, Edinburgh, 1892-3, ii, 91.
13. Greenfield: Brit. Med. Jour., 1893, ii, 1261.
14. Edmunds: Lancet, London, 1901, i, 1317, 1381, 1449.
15. Farner: Virchow's Arch. f. path. Anat., 1896, cxliii, 509.
16. Von Hansemann: Berl. klin. Wchnschr., 1905, No. 44a 65.
17. Hirschlaff: Ztschr. f. klin. Med., 1899, xxxvi, 200.
18. MacCallum: Johns Hopkins Hosp. Bull., 1905, xvi, 287.
19. Ewing: Tr. Assn. Am. Phys., 1906, xxi, 567.
20. Lewis: Surg., Gyn. and Obst., 1906, iii, 476.
21. Wilson: Am. Jour. Med. Sc., 1908, cxxxvi, 851.

sent the most familiar type of extensive active hyperplasia in man, but by no means the most frequent one, since identical histological changes are observed in the prenatal, puberty and pregnancy thyroid enlargements. To sum up: The thyroid changes in all forms of active hyperplasia are characterized by an increase in the blood supply and the lymphatic drainage; a decrease in the stainable colloid; marked hypertrophy and hyperplasia of the follicular epithelium; a variable increase in the stroma, and frequently deposits of lymphoid tissue here and there throughout the stroma.

In addition to the necessity of establishing two series of hyperplasias —normal and colloid, as above mentioned—and the ready explanation it affords in many histological pictures of hyperplasia, there is perhaps another factor that modifies our interpretation of hyperplasias which has not been sufficiently emphasized in the published descriptions. It is the occurrence of atrophic changes. This type of atrophy seems to differ from simple cell atrophy in that there is a marked disturbance in the nucleus-plasma relationship, and, as it has been observed only in glands with marked hyperplasia from subjects that during life showed clinical signs of myxedema or cretinism, its significance will be discussed along with these diseases.

III. COLLOID GLANDS*

The third great natural division of thyroid changes are the colloid glands (goiters). In our human series it will be noticed (see Tables 8 and 1) that there are 25 colloid glands and 23 normal. This surprising proportion of colloid glands is due to two factors. First, in goitrous districts hyperplasias are much more common than normal glands (the proportions of hyperplasia to normal in our normal series' collection being 53 to 3 for dogs, 14 to 19 for sheep, 6 to 18 for pigs, 20 to 17 for cattle and 23 to 23 for man) and all reverted hyperplasias are colloid glands (goiters). Second, we have called all glands colloid that show any evidence of having previously undergone active hyperplasia. Thus there are many glands that, as regards size, shape, color, consistency, colloid and histological appearance, would ordinarily be considered normal. They are physiologically normal, but they show the marks of a previous hyperplasia, and for sake of strict anatomical analysis it is necessary to recognize these anatomical differences.

Pure colloid glands (goiters) present no essential differences in any of the animals examined. They differ essentially from normal glands in all these animals only in size (though, as has just been pointed out, they may be no larger than normal) and in showing the vestiges of pre-

* See Figure 7.

vious hyperplasia. These marks of previous hyperplasia, however, are well-defined and characteristic. Their prominence in any given specimen depends on the degree and duration of hyperplasia and the length of time since the reversion occurred. These changes are to be found in the size and shape of the follicles, in the presence of sprig-like projections into the follicles in the more recent involutions (reversions), in the blood and lymph vessels, and in the stroma and capsule. The epithelium is normal (flat cubical), the stroma is increased, although to this statement there are exceptions depending on the extent of the fibrosis occurring during the active hyperplasia and the extent of the absorption which normally occurs during the process of reversion. Thus we have seen markedly cretinoid pups' thyroids, in which the stroma was so increased that the scattered thyroid follicles gave the gland the appearance of the endometrium, so resolve in the course of a month following the administration of iodin as to have all the appearances of a pure colloid gland with normal stroma. Such cases illustrate how rapidly the body can adjust physiological defects. The thickened thyroid capsule is likewise the inheritance from the preceding hyperplasia and varies greatly in thickness in different specimens. The arterial walls are always thickened and histologically show an obliterating endarteritis similar to that seen in the involuting thymus or uterus. Calcification is very common in these thickened walls, and even the veins may contain calcareous deposits in their walls. The most striking change in the veins and lymphatic trunks is the great lessening in their caliber. This is associated with some thickening of their walls. The stainable colloid is normal in appearance and distribution in the follicles. The follicles are in general much larger than in normal glands, but this depends on the degree of hyperplasia preceding the involution (reversion), and perhaps also on other as yet ill-defined factors, as, for example, the cause of reversion and the duration of the process. If only a hypertrophy has preceded the involution (reversion), then it is scarcely possible to distinguish such a gland from normal. We have met several glands of which we could neither convince ourselves that the structure was normal nor offer definite proof of a previous hyperplasia. These glands we have called "normal-colloid" and have separated them for analytic purposes. The sprig-like projections into the follicles are the remnants of the infoldings or plications occurring during the preceding hyperplasia and there is evidence that these sprigs are slowly effaced in long-standing colloid glands (goiters).

Only brief mention in the way of explanation of the other divisions of the classification can be made here, inasmuch as they are not primarily concerned in the production of goiter and will be discussed in a later publication.

IV. ATROPHY

Atrophy is a normal senile process. The thyroid is most active in youth, as is also goiter formation. True goiter rarely develops after 45 years of age.[22] Simple atrophy also occurs in many of the chronic diseases, and is particularly associated with chronic pulmonary tuberculosis. The special forms of atrophy leading to colloid glands, and consequent upon the hypertrophies and hyperplasias of puberty, menstruation and pregnancy, are best considered involutions (reversions).

The form associated clinically with the symptom-complex of myxedema, first recognized by Gull[23] and later carefully described by Ord[24] and Hun and Prudden,[25] is of particular interest in that it is a form of atrophy occurring in spite of attempts at hyperplasia and is apparently the result of sustained thyroid stimulation without intervening periods of physiological rest. It is coming to be more recognized that this form of atrophy is practically always preceded by hyperplasia, with or without the symptom-complex of exophthalmic goiter. This change is seen particularly in cases of exophthalmic goiter that are passing over into myxedema. Briefly, the histological changes are as follows: The epithelial cells lose the regular and uniform type characteristic of the usual hyperplasia and become irregular in size and shape. There is desquamation and piling up of the epithelial cells in the vesicles. The nuclei are in general enlarged, hyperchromatic and irregular in size and shape. Nuclear figures are observed, but the new formation of cells is not sufficient to offset the cell degeneration and the vesicles become smaller. The surrounding fibrous tissue is relatively, perhaps absolutely, increased, and, as the vesicles are reduced in size, they are more and more widely separated. The interstitial cirrhosis, we believe, is secondary and consequent on the destruction of the epithelial elements. We have frequently observed the milder forms of this type of atrophy in exophthalmic goiter thyroids and feel sure that it is more common than the literature reports indicate.

V. REGENERATION

Except for normal replacing of cells as they die—a process which is continually going on in most glandular tissues—regeneration is a compensatory process and hence is more aptly considered a part of the general group of hyperplasias. Regeneration occurs following partial destruction

22. Horsley: Brit. Med. Jour., 1892, i, 215.
23. Gull: Tr. Clin. Soc., London, 1874, vii, 180.
24. Ord: Med.-Chir. Tr., London, 1878, lxi, 57.
25. Hun and Prudden: Am. Jour. Med. Sc., 1888, xcvi, 140.

or removal of the thyroid, as has been amply shown for man and animals.[26]

The new-formed tissue may remain normal in structure, as occurs in young animals after partial removal with the administration of iodin, or it may take on the characteristics of true spontaneous hyperplasia, as in similar cases of partial removal without the administration of iodin. The two groups of "Regeneration" and "Hyperplasia" are so nearly a part of each other that it is impossible to distinguish sharply between them. To say that regeneration stops when the thyroid tissue has attained its normal amount is not in accord with all the known facts. The normal gland shows considerable variation in different subjects and, besides, there are at least two factors concerned: the first is the actual number of cells necessary to perform the thyroid functions under favorable conditions of nutrition and metabolism, and the second factor is the degree of cell proliferation which may occur in conditions of malnutrition or disturbed nutrition. Thus the statement sometimes made that compensatory regeneration does not exceed the normal size of the gland[27] is not in accord with our present knowledge, for the reason that the extent of the cell proliferation in the thyroid depends on the physiological requirements of the animal and this can be markedly influenced by diet, iodin, etc.

VI. DEGENERATIONS

Degenerations include calcareous, hyaline and amyloid changes and are never seen apart from other pathological processes, as hemorrhage, cyst formation, etc. These changes are very frequently seen in old colloid goiters, but they are always secondary changes and are never essential parts of the colloid transformation. Pure colloid goiters are not degenerative processes, as they have long been considered. They are more allied to the atrophies and are, properly speaking, involutions, since it is now definitely known that they obey all the known biological laws of normal glands (Marine and Lenhart[2]).

VII. INFLAMMATIONS

Apart from a general view that all goiter is inflammatory in nature, true inflammations as we regard them to-day are rare.[28] They may, how-

26. Wagner: Wien. med. Bl., 1884, vii, 771. Schiff: Arch. f. exper. Path. u. Pharmakol., 1884, xviii, 25. Halsted: Johns Hopkins Hosp. Rep., 1896, i, 373. Welch: Med. Rec., New York, 1888, xxxiv, 368. Horsley: Brit. Med. Jour., 1892, i, 215. Ribbert: Virchow's Arch. f. path. Anat., 1889, cxvii, 151. Sulzer: Ztschr. f. Chir., 1893, 191.

27. MacCallum, W. G.: The pathology of exophthalmic goiter. Jour. Am. Med. Assn., 1907, xlix, 1158.

28. Ewald, C.: München. med. Wchnschr., 1896, xliii, 634.

ever, occur in the course of many of the infectious diseases, as lues, tuberculosis, typhoid, influenza, etc. Inflammation has frequently followed injuries, as in the old treatment of goiter by iodin and iron injections.[29]

VIII. TUMORS

The most frequent tumor of the thyroid is the fetal adenoma, as described by Billroth,[30] Bloodgood,[31] and others. These are usually small, frequently multiple and may attain the size of one's fist. There are apparently several types or phases of these tumors, ranging from the type closely resembling fetal thyroid which gave rise to the name, to the well-differentiated colloid-containing form. Likewise these tumors are known to undergo (reversion) involution to the colloid or quiescent state, in which they can not be differentiated from ordinary colloid goiter except for the smaller size of the alveoli and their complete encapsulation.

Aside from the above-described form one finds encapsulated adenomatous growths of well-differentiated thyroid tissue growing, in some instances, apparently independently of the rest of the thyroid gland and histologically resembling the well-differentiated cells of ordinary thyroid hyperplasia. Without any definite evidence, we are inclined to look on them as closely related to the fetal adenoma, being only a fully differentiated type.

Carcinoma of the thyroid is difficult of diagnosis microscopically. It has long been known that not infrequently one finds apparently benign types of thyroid tumor in what are undoubtedly metastases, and also there are cases reported in which metastatic thyroid tissue has been found with no evidence of a primary growth in the thyroid. Thus it is probable that we have not recognized some of these tumors, but, on the other hand, it is probable that there are tumors reported as carcinoma that are not. In our experience, however, carcinoma of the thyroid in man is rare. It would appear to be in some way related to the frequency of goiter, and even associated with goiter itself. Pick,[32] working with the carcinoma of brook trout, was inclined to such a view. We have observed two types of thyroid carcinoma. One, histologically, closely resembles the fetal adenoma tissue and might be called malignant fetal adenoma. The other preserves the characteristics of differentiated thyroid tissue. Seven cases of carcinoma of the thyroid in old dogs have come to our notice. Three of the cases had lung metastases. In all there had been

29. Semon: Brit. Med. Jour., 1885, i, 715.
30. Billroth: Arch. f. Anat. Physiol. u. wissensch. Med., Berlin, 1856, 144.
31. Bloodgood: Surg., Gyn. and Obst., 1906, ii, 121.
32. Pick: Berl. klin. Wchnschr., 1905, xlii, 1536.

long-standing goiters. In none was there accompanying sarcoma, as has been reported by Schöne.[33] The epithelial changes were similar to those described by the above observer.

We have seen one case of lymphangioendothelioma probably originating in the thyroid, but no case of true sarcoma.

IX. COMPLICATIONS

Hemorrhage and its sequelæ are the most frequent secondary changes in goiter. Hemorrhage occurs more commonly in the colloid phase. It is dependent on trauma and overdistention of the alveoli with subsequent rupture of their walls.[34] Hemorrhages occur in all animals in which colloid glands are seen and their relative natural frequency probably is the same, although it seems more common in dogs. Trauma, as in fighting and sudden violent exertions causing venous engorgement, perhaps plays an important rôle in dogs. Cysts are the most important sequels of hemorrhages and we are inclined to believe with Bradley[35] that the great variety of cysts seen in the thyroid are probably primarily of hemorrhagic origin. Occasionally small hemorrhages are seen in otherwise histologically normal glands. Hydatid cysts are occasionally reported.

It seems clear from the preceding anatomical discussion that in the development of the true goiter only three groups are primarily involved—viz.: (1) normal glands, (2) hyperplasias, and (3) colloid glands. The variety of secondary and complicating changes, as atrophy, degeneration, regeneration, cyst formation, etc., is almost infinite. Of the three great groups, normal glands are the most important to have firmly established, since they form the base to which all other changes must be referred for comparison.

Active hyperplasias comprise a gradation from the nearly normal or colloid gland (true hypertrophy) to the extreme degrees of hyperplasia seen in exophthalmic goiter. The histological appearance of a given specimen, apart from the degree of hyperplasia and whatever secondary changes may be present, is modified by two important factors—viz: (1) the number of times the gland has returned to the colloid state (reversion), as, for example, in the case of repeated pregnancies when during each pregnancy there was active hyperplasia and during each interval there was a return to the colloid state; and (2) the length of time active hyperplasia has continued without a period of rest. Thus, in the marked hyperplasias of exophthalmic goiter or of cretins,[36] we see apparent over-

33. Schöne: Virchow's Arch. f. path. Anat., 1909, excv, 169.
34. Wölfler: Arch. f. klin. Chir., 1883, xxix, i, 754.
35. Bradley: Jour. Exper. Med., 1896, i, 401.
36. McGarrison: Proc. Roy. Soc. Med., 1908, ii, No. 3, Med. Section, p. 1.

growth of fibrous tissue with very striking irregularities and disturbances in the nucleus-plasma relations of epithelial cells. These nucleus-plasma disturbances in cretin dogs are able to right themselves when iodin is administered, and in such glands one may then produce a regular, uniform, compensatory hyperplasia by partial removal. Colloid glands are but exaggerations of all the structures of normal glands, depending on the degree of active hyperplasia preceding the involution (reversion). It is our belief that all colloid glands have been preceded by active hyperplasia, and that passive dilatation of the alveoli due to continued secretory activity and obstruction to the lymphatic drainage is of secondary importance. Rupture of the alveoli and other secondary and complicating changes may occur. So also a colloid gland may undergo secondary active hyperplasia differing essentially in no way from the primary form occurring in a normal gland.

RELATION OF SEX AND AGE OF THE ANIMAL AND SIZE OF THE GLAND TO HISTOLOGIC STRUCTURE

It is usually stated by anatomists that the normal human thyroid is larger in infants and children and in females than in later periods of life or in males—i. e., larger in relation to the body weight. Other than this, sex and age have no particular relation to normal glands. The normal gland at birth is well differentiated into colloid-containing vesicles in the sheep, dog, ox and man. As a class normal glands are the smallest met. The average weights in our series were 2.08 gm. for dogs, 12 gm. for oxen, 6.9 gm. for sheep, and 24 gm. for man.[37]

Active hyperplasias in man are definitely associated with age and sex. Sex has no important relation to the hyperplasias in the dog, ox, sheep and pig. In man also sex is not a modifying factor in the hyperplasias of infancy and childhood. Starting with puberty, however, active hyperplasia is more common in females. The clinical incidence is variously estimated[38] from 3 to 1 to 6 to 1. The actual or anatomical incidence in our series is modified by the larger proportion of males in the autopsy material and the larger proportion of females in the surgical material; and also by the fact that any thyroids showing anatomical complications were not used. These factors make deductions worthless. The metabolic disturbances associated with the establishment of menstrual functions, with menstruation, with pregnancy and lactation, and with the meno-

37. Wondenberg (Virchow's Arch. f. path. Anat., 1909, cxcvi, 107) has reported much higher weights for normal glands in these animals.

38. Dock: Osler's Modern Medicine, 1909, vi, 404.

pause are particularly associated with goiter development. Nothing is known definitely regarding the physiological nature of the disturbances which stimulate the thyroid to hyperplasia at these particular periods.

Age is a factor in the hyperplasias common to all animals. They are more frequently observed in the young, when the thyroid is normally functionally more active. This is particularly true of the lower animals. In man it is also true, but there are modifying factors not sufficiently prominent in the lower animals, as, for example, the sexual cycle and the disturbances leading to exophthalmic goiter, which are particularly associated with goiter formation, and which modify the age limitations of human goiter.

As regards the size of the glands, it may be stated that the size varies with the degree of hyperplasia. There are exceptions to this rule, especially in man. These exceptions most likely depend on a more complicated etiology and life cycle in human goiters..

Colloid glands of the lower animals have no noteworthy relation to sex. Sex is also not a factor in human colloid glands before puberty. After puberty colloid glands are more common in females, for the reason that hyperplasias are more common.

Age is a very important factor in colloid glands of all animals. They are always sequels of active hyperplasia and therefore occur at correspondingly later periods of life. The size of the colloid gland depends mainly on the degree of hyperplasia preceding the involution (reversion). Other factors, as repeated hyperplasia, medication and lymphatic obstruction inducing passive dilatation of the vesicles, operate, to a less extent, to modify the size. Thus colloid glands may be no larger than normal glands, or they may attain the size of the largest goiters.

Summing up, it is seen that age and sex bear no important relation to normal glands. In the hyperplasias age is of great importance, while sex is an important factor only in those hyperplasias in man occurring during and after puberty. In colloid glands age is also a very important factor in all animals—while sex is important in the human forms occurring during and after puberty.

As regards size, normal glands as a class are the smallest observed. In the hyperplasias the size depends on the degree of hyperplasia and in colloid glands the size as a rule depends on the degree of the preceding hyperplasia. Thus, while the size of the gland, the age and the sex of the animal are related to the gland structure and its variations, they can be considered as only secondary and accompanying factors to the fundamental causes in the etiology of goiter.

IODIN DETERMINATION

Iodin determinations have been made on 161 different human thyroids, of which 96 are used in the following 14 tables, where they have been classified according to their histology. The method used in determining the iodin content is fully described in an earlier publication (Marine and Williams[4]) and has been used throughout without modification. We have used several modifications of the method proposed from time to time, but all our observations by means of these modifications and of controls in thirty-one cases have convinced us that the above method will not lead to erroneous conclusions if only the iodin content in relationship with the histological structures is considered. The method and the proposed modifications are not quantitatively accurate.

The three natural anatomical groups—viz: (1) normal thyroids, (2) colloid thyroids, and (3) actively hyperplastic thyroids, with the arbitrary subdivision of the latter group—are also the same as those previously used and described.

The anatomical standards being the same or as nearly the same as it was possible to make them, we have also brought forward the iodin determinations in dog, sheep, pig and ox thyroids for comparison.

One important addition to the earlier recorded observations will be noted in that the human colloid series is nearly complete and the canine colloid series is sufficiently complete to parallel the normal series in these two animals and will be discussed with equal emphasis.

The reasons—anatomical, chemical (iodin) and biological—for establishing a colloid series parallel with the normal series have already been set forth at some length (Marine and Lenhart[2]) and need not be reviewed here except to state that the only essential difference between normal and colloid glands is that colloid glands have at some time undergone active hyperplasia, while strictly normal glands have never undergone such hyperplasia.

As above stated, 161 different human thyroids have been analyzed for iodin, of which 111 were autopsy specimens and 50 surgical specimens. Of these only 96, of which 77 were autopsy specimens and 19 surgical specimens, have been included in the tables of analysis. Of the 34 (30.6 per cent.) autopsy specimens not used 11 were from children under two years; 10 from old subjects showing histologically marked senile atrophy; 2 contained multiple small fetal adenomata; 3 showed marked atrophy with fibrosis associated with chronic pulmonary tuberculosis; 6 had, to our knowledge, been fed large amounts of iodin-containing compounds during the last few months of life; 1 showed marked simple atrophy without assignable cause (myxedema), and 1 specimen had been handled

for demonstration purposes. Of the 31 (62 per cent.) surgical specimens not used, 11 had been previously treated with iodin containing compounds; 14 were discarded on account of old hemorrhagic-cystic-degenerative changes; 5 were discarded on account of fetal adenomata, and 1 for malignant tumor (endothelioma).

The fact that 65 (40.4 per cent.) could not, for one or another reason above mentioned, be included in the tables clearly shows that no conclusions can be drawn from a limited material even if this material be from autopsies with no clinical suspicion of thyroid disease. With surgical material this is especially true. Our percentage (38 per cent.) of uncomplicated surgical specimens is unusually high and is due to the presence of several uncomplicated cases of exophthalmic goiter. We have pointed this out specifically here because in all publications thus far recorded on the relation of iodin to human goiter the complicating factors have not been taken into account. We also feel certain that a larger series than we have here recorded, whether autopsy or surgical, would modify the figures here given, particularly if the district from whence the glands were taken were goitrous, while, on the other hand, a smaller series would give more uniform results if seacoast glands were used.

Pure types of histological changes only can be used, because, in the present state of our knowledge, we can not discount for the multiple anatomical complicating factors so common in the thyroid and which have already been alluded to.

Then, too, besides the anatomical complications, there are a great group of metabolic (physiological) changes producing effects on the structure or secretion of the gland either too slight or too temporary to be accurately ascertained or discounted. We refer to such conditions as variations depending on the seasons of the year,[39] on the sexual functions, on rest, on menstruation, on pregnancy, on climatic variations,[40] on food variations, etc.

Thus by eliminating all known untoward factors there are still present many uncertainties which can not be avoided at present and render conclusions from such data dangerous except those on the general relation of iodin with the structure and physiology of the thyroid.

The individual cases of the normal and colloid human series have been tabulated separately (Tables 15 and 16). It will be noticed that in only a few cases is the iodin content calculated for the fresh gland. This is due to the fact that the other specimens had been preserved in 10 per cent. formalin from one to seven days before being used. This factor, as

39. Koch, F. C.: Discussion on Hunt and Seidell's paper on commercial preparations. Jour. Am. Med. Assn., 1908, li, 1389.

40. Sawyer, J. P.: New York Med. Jour., 1907, lxxxvi, 68.

Williams[41] has shown, makes little or no difference as regards the iodin content per gm. of dried gland.

It was impossible to get actual weights of the thyroids in the fresh condition in most instances and we have only indicated roughly their size by the terms "normal," "slightly enlarged," "moderately enlarged" and "markedly enlarged." Thus thyroids from adults weighing between 20-30 gm. we have called "normal," between 30 and 50 "slightly enlarged," between 50 and 100 "moderately enlarged," and over 100 gm. "markedly enlarged."

Since the iodin content in relationship with the individual anatomical groupings has been discussed at length in earlier publications, they will here be discussed collectively in relationship with the basic anatomical groups—normals, colloids and the two series of hyperplasias.

NORMAL GLANDS *

Normal glands have the highest mean and average iodin content per gram. This is true for all animals thus far examined. In our twenty-three human specimens the highest iodin content per gram of dried gland was 3,691 mgm.; the lowest 1,307 mgm. The significance and explanation of this great variation in histologically normal glands becomes of greater importance when one notes that it is also seen with the dog, sheep, ox and pig thyroids. Whether it indicates variations in the intake or variations in the consumption within the organism, or both, is not clear. The evidence at present available indicates that the consumption of iodized protein in the body is the most constant. Thus it is known that the administration of very small amounts of iodin is followed by its rapid storage in the gland in all animals, the rapidity of the process depending on the degree of hyperplasia (therefore, on the lack of iodin). On the other hand, it is known that the withholding of iodin, as by a fresh meat diet,[42] causes a slow loss of iodin from the gland. That these variations (1.307-3.691 mgm.) are not due to accumulation of iodin, either by accident or to an effort to render inert the piosonous properties of iodin, is both true and false. Thus there are differences that depend purely on the accidental content of the food in iodin. It is also probably true that the iodin, so long as it remains in the thyroid, is inert (to the host), because it represents merely the stored iodin, or the factor of safety. On the other hand, broadly interpreted, none of the iodin in the thyroid is inert or accidental, inasmuch as it is stored there for the

41. Marine, D., and Williams, W. W.: The relation of iodin to the structure of the thyroid gland. THE ARCHIVES INT. MED., 1908, i, 378.

* See Tables 1 and 15.

42. Baumann: München. med. Wchnschr., 1896, xliii, 309.

purpose of later becoming available to the organism. All observers, from whatever angle they approach the question, have concluded that the iodin content determined the physiological activity of the protein (thyreoglobulin). Thus Roos[43] observed that the increased nitrogen excretion induced by feeding thyreoglobulin depended on its iodin content. Hunt[44] has found that the protection offered to mice against acetonitrile poisoning depends on the iodin content. We have shown the biological fact that if the iodin falls below a quite constant level the gland undergoes characteristic and constant histologic changes, while, if iodin is given, these changes either do not occur or, if they have started, they are arrested. As one of us[45] has previously indicated, we believe that the organism retains iodin in the same way that it retains iron and calcium, etc., and that the difference between the greatest amount of either iodin, iron or calcium and the least amount that may be found in the animal to be compatible with the maintenance of normal histological structure of the tissues immediately concerned with their storage and elaboration, represents the excess of intake over consumption, or the true physiological factor of safety.[46]

NORMAL SERIES—VARIOUS ANIMALS

TABLE 1.—NORMAL GLANDS *

Animal.	No. Cases.	—Iodin Per Gm., Dried.— E.	M.	A.	—Iodin Per Gm., Fresh.— E.	M.	A.
Sheep	19	4.614 1.247	2.288	2.467	1.318 0.318	0.694	0.686
Dog	3	4.722 1.990	3.205	3.322	1.064 0.512	0.757	0.777
Pig	18	4.153 1.538	2.412	2.515	1.456 0.425	0.778	0.884
Ox	17	4.768 2.730	3.254	3.461	1.592 0.892	1.069	1.117
Man	23	3.691 1.307	2.153	2.171	0.451 0.310	0.403	0.402

* In this and the following tables, E stands for extreme, M for mean, and A for average. Iodin figures are in mgm.

43. Roos: Ztschr. f. physiol. Chem., 1899, xxviii, 40.

44. Hunt: The relation of iodin to the thyroid gland. Jour. Am. Med. Assn., 1907, xlix, 1323.

45. Johns Hopkins Hosp. Bull., 1907, xviii, 359.

46. Meltzer, S. J.: The Harvey Lectures, 1906-07. Lippincott, Philadelphia, 1908, p. 139.

TABLE 2.—Normal-Early Glandular Hyperplasia

Animal.	No. Cases.	—Iodin Per Gm., Dried.— E.	M.	A.	—Iodin Per Gm., Fresh.— E.	M.	A.
Sheep	1	....	.....	0.677	....	.....	0.176
Dog	7	1.296 0.483	0.815	0.879	0.318 0.018	0.153	0.174
Pig	1	....	.....	1.230	....	.....	0.337
Ox	7	2.676 2.000	2.307	2.317	0.726 0.482	0.653	0.628
Man	4	0.984 0.615	0.807	0.803	0.216 0.196	.....	0.206

TABLE 3.—Early Glandular Hyperplasia

Animal.	No. Cases.	—Iodin Per Gm., Dried.— E.	M.	A.	—Iodin Per Gm., Fresh.— E.	M.	A.
Sheep	..	....	.....	.....	....	.....	.....
Dog	9	1.028 0.243	0.654	0.625	0.235 0.063	0.113	0.139
Pig	2	1.158 1.046	.....	1.102	0.291 0.279	.....	0.285
Ox	3	2.186 1.123	1.630	1.646	0.615 0.314	0.456	0.462
Man	5	1.077 0.738	0.877	0.895	....	.....	.....

TABLE 4.—Early-Moderate Glandular Hyperplasia

Animal.	No. Cases.	—Iodin Per Gm., Dried.— E.	M.	A.	—Iodin Per Gm., Fresh.— E.	M.	A.
Sheep	1	....	.....	0.548	....	.....	0.131
Dog	1	....	.....	0.262	....	.....	0.082
Pig	3	0.846 0.769	0.769	0.795	0.241 0.198	0.233	0.224
Ox	5	1.030 0.969	1.000	1.000	0.252 0.205	0.222	0.226
Man	3	0.738 0.406	0.554	0.566	....	.....	.....

TABLE 5.—Moderate Glandular Hyperplasia

Animal.	No. Cases.	—Iodin Per Gm., Dried.— E.	M.	A.	—Iodin Per Gm., Fresh.— E.	M.	A.
Sheep	1	.....	.....	0.400	.....	.....	0.091
		.....			.....		
Dog	9	0.854	0.345	0.368	0.136	0.076	0.078
		0.101			0.026		
Pig	..	.....	.....	.....	.....	.....	.....
		.....			.....		
Ox	..	.....	.....	.....	.....	.....	.....
		.....			.....		
Man	2	0.807	.....	0.711	.....	.....	.....
		0.615			.....		

TABLE 6.—Moderate-Marked Glandular Hyperplasia

Animal.	No. Cases.	—Iodin Per Gm., Dried.— E.	M.	A.	—Iodin Per Gm., Fresh.— E.	M.	A.
Sheep	5	0.092	0.024	0.031	0.014	0.003	0.004
		0.000			0.000		
Dog	9	0.660	0.231	0.283	0.109	0.042	0.055
		0.058			0.011		
Pig	..	.....	.....	.....	.....	.....	.....
		.....			.....		
Ox	..	.....	.....	.....	.....	.....	.....
		.....			.....		
Man	2	0.480	.....	0.406	.....	.....	.....
		0.332			.....		

TABLE 7.—Marked Glandular Hyperplasia

Animal.	No. Cases.	—Iodin Per Gm., Dried.— E.	M.	A.	—Iodin Per Gm., Fresh.— E.	M.	A.
Sheep	6	0.036	0.000	0.006	0.006	0.000	0.001
		0.000			0.000		
Dog	18	0.640	0.073	0.114	0.123	0.014	0.023
		0.008			0.002		
Pig	..	.....	.....	.....	.....	.....	.....
		.....			.....		
Ox	5	0.270	0.215	0.189	0.062	0.042	0.041
		0.077			0.016		
Man	7	0.584	0.292	0.323	0.115	0.109	0.095
		0.118			0.060		

COLLOID SERIES—VARIOUS ANIMALS

TABLE 8.—Colloid Glands

Animal.	No. Cases.	—Iodin Per Gm., Dried.— E.	M.	A.	—Iodin Per Gm., Fresh.— E.	M.	A.
Sheep	3	3.691 1.769	3.529	2.996	1.027 0.455	0.974	0.818
Dog	8	3.608 0.846	1.816	1.985	1.039 0.132	0.406	0.459
Pig	2	2.768 1.938	.....	2.353	0.805 0.557	.....	0.681
Ox	..	....	.....	.....	....	.....	.....
Man	25	3.914 0.784	1.769	1.996	0.798 0.304	0.479	0.515

TABLE 9.—Colloid-Early Glandular Hyperplasia

Animal.	No. Cases.	—Iodin Per Gm., Dried.— E.	M.	A.	—Iodin Per Gm., Fresh.— E.	M.	A.
Sheep	4	1.000 0.461	0.853	0.792	0.282 0.138	0.201	0.206
Dog	6	1.443 0.431	0.953	0.945	0.302 0.125	0.221	0.217
Pig	..	....	.....	.....	....	.....	.....
Ox	..	....	.....	.....	....	.....	.....
Man	8	0.887 0.461	0.823	0.777	....	.....	0.208

TABLE 10.—Colloid-Early-Moderate Glandular Hyperplasia

Animal.	No. Cases.	—Iodin Per Gm., Dried.— E.	M.	A.	—Iodin Per Gm., Fresh.— E.	M.	A.
Sheep	..	....	.....	.....	....	.....	.....
Dog	2	0.692 0.560	.....	0.626	0.167 0.114	.....	0.140
Pig	..	....	.....	.....	....	.....	.....
Ox	..	....	.....	.....	....	.....	.....
Man	2	0.600 0.446	.....	0.523	....	.....	.....

TABLE 11.—COLLOID-MODERATE GLANDULAR HYPERPLASIA

Animal.	No. Cases.	—Iodin Per Gm., Dried.— E.	M.	A.	—Iodin Per Gm., Fresh.— E.	M.	A.
Sheep	..	.....	.....	.....	.....	.....	.....
		.....			.....		
Dog	3	0.554	0.446	0.423	0.099	0.098	0.085
		0.269			0.059		
Pig	..	.....	.....	.....	.....	.....	.....
		.....			.....		
Ox	..	.....	.....	.....	.....	.....	.....
		.....			.....		
Man	7	0.492	0.366	0.355	0.116	.....	0.090
		0.184			0.064		

TABLE 12.—COLLOID-MODERATE-MARKED GLANDULAR HYPERPLASIA

Animal.	No. Cases.	—Iodin Per Gm., Dried.— E.	M.	A.	—Iodin Per Gm., Fresh.— E.	M.	A.
Sheep	..	.....	.....	.....	.....	.....	.....
		.....			.....		
Dog	1	.....	.....	0.128	.....	.....	0.030
		.....			.....		
Pig	..	.....	.....	.....	.....	.....	.....
		.....			.....		
Ox	..	.....	.....	.....	.....	.....	.....
		.....			.....		
Man	..	.....	.....	.....	.....	.....	.....
		.....			.....		

TABLE 13.—COLLOID-MARKED GLANDULAR HYPERPLASIA

Animal.	No. Cases.	—Iodin Per Gm., Dried.— E.	M.	A.	—Iodin Per Gm., Fresh.— E.	M.	A.
Sheep	..	.....	.....	.....	.....	.....	.....
		.....			.....		
Dog	1	.....	.....	0.115	.....	.....	0.022
		.....			.....		
Pig	..	.....	.....	.....	.....	.....	.....
		.....			.....		
Ox	..	.....	.....	.....	.....	.....	.....
		.....			.....		
Man	..	.....	.....	.....	.....	.....	.....
		.....			.....		

TABLE 14.—NORMAL-COLLOID GLANDS.

Animal.	No. Cases.	—Iodin Per Gm., Dried.— E.	M.	A.	—Iodin Per Gm., Fresh.— E.	M.	A.
Sheep	..	.....	.....	.....	.....	.....	.....
		.....			.....		
Dog	..	.....	.....	.....	.....	.....	.....
		.....			.....		
Pig	..	.....	.....	.....	.....	.....	.....
		.....			.....		
Ox	..	.....	.....	.....	.....	.....	.....
		.....			.....		
Man	8	3.230	1.653	1.942	.....	.....	.....
		1.100			.....		

HYPERPLASTIC GLANDS

The two series of hyperplastic glands, "normal" and "colloid," while separate and distinct anatomically, are alike chemically (iodin). That is, the iodin varies inversely with the degree of active hyperplasia, whether the hyperplasia occurs on the basis of a normal or of a colloid gland. This is illustrated very clearly in the curves (Figs. 8 and 9) of the two series. Here it is seen that the general trend of the curve is the same for all the animals examined, and also for both the normal and the colloid series. There are twenty-three cases of active hyperplasia in the normal series and seventeen cases in the colloid seris.

1. First taking up the hyperplasias of the normal series:* The most striking and perhaps the most important fact brought out is the great drop in the iodin content that occurs before histological changes are noticed. This is equally true of all the animals (see normal series' curve, Fig. 8). Reference to Table 15 shows that the lowest normal iodin content (1,307 mgm.) is well above the highest iodin content (1.077 mgm.) of the hyperplasias. This is also true of all the ainmals. It indicates that there is a quite constant lower limit in the iodin content necessary for the maintenance of normal gland structure and if the iodin falls below this limit, hypertrophic or hyperplastic changes begin. In our normal thyroid series the lowest iodin content per gram of dried gland associated with normal structure, and the highest iodin content associated with hyperplastic changes run as follows: For man, 1.307 and 1.077; for the dog, 1.990 and 1.296; for the sheep, 1.247 and 0.677; for the ox, 2.730 and 2.676, and for the pig, 1.538 and 1.158 mgm. Just as the earliest histological variations from the normal are the most

* See Tables 1, 7 and 15.

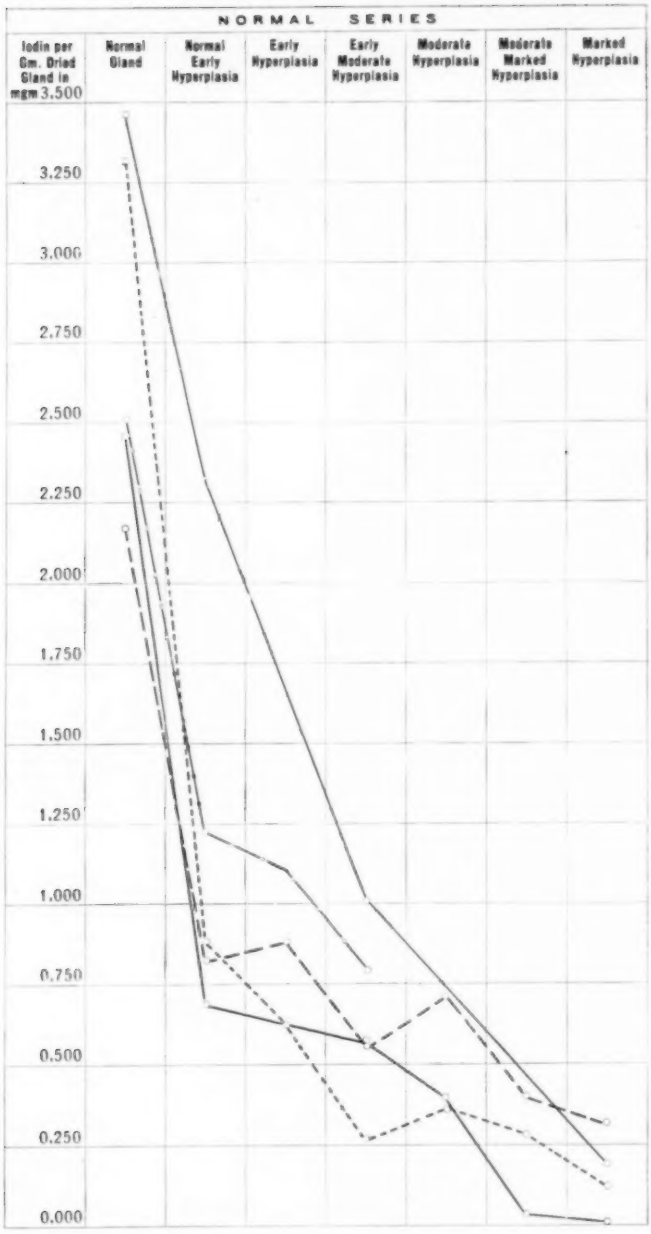


Fig. 8.—Curves compiled from the average iodin contents per gram of dried gland of the normal series of hyperplasias. The solid line represents the curve for the ox, the dotted line the curve for the dog, the line composed of short and long dashes the curve for the sheep, the line with short dashes the curve for man, and the line composed of long dashes and circles the curve for the pig.

TABLE 15.—NORMAL SERIES—MAN

Series No.	Age.	Sex.	Autopsy or Surgical.	Anatomical or Clinical Diagnosis.	Size of Gland.	Visible Colloid.	Normal.	Colloid.	Early.	Moderate.	Marked.	Per ct. Water.	Iodin, per gm., Dried.*	Iodin, per gm., Fresh.*	Remarks.
H-232	45	M.	S.	Exophthalmic goiter	?	Absent	..	..	..	..	+	..	0.118	.....	Slight signs of myxedema.
H-364	31	F.	S.	Exophthalmic goiter	?	Absent	..	..	..	..	+	..	0.125	.....	Definite signs of myxedema.
H-251	25	M.	S.	Exophthalmic goiter	?	Absent	..	..	..	..	+	..	0.277	0.060	
H-267	20	M.	S.	Exophthalmic goiter	?	Absent	..	..	..	..	+	..	0.292	.....	Very severe type; marked lymphoid hyperplasia; autopsy.
H-237	41	F.	A.	Pernicious anemia	Slightly enlarged.	Absent	..	..	..	..	+	..	0.323		
H-214	37	F.	S.	Exophthalmic goiter	?	Visible.	..	..	..	..	+	..	0.544	0.109	Definite signs of myxedema.
H-222	50	F.	S.	Exophthalmic goiter	?	Absent	..	..	..	..	+	..	0.584	0.115	
H-226	35	M.	A.	Cerebrospinal meningitis	?	Absent	..	..	..	+	+	..	0.332		
H-343	10	M.	A.	Acute rheumatic endocarditis	Slightly enlarged.	Visible.	..	..	..	+	+	..	0.480	.....	Negro: status lymphaticus.
H-325	42	M.	A.	Nephritis—cerebral hemorrhage	Slightly enlarged.	Visible.	..	..	..	+	..	..	0.615		
H-270	35	M.	S.	Exophthalmic goiter	?	Visible.	..	..	..	+	..	..	0.807		
H-258	5	M.	A.	Hemorrhagic purpura and lymphatic leukemia.	Slightly enlarged.	Visible.	..	..	+	+	..	..	0.406		
H-368	24	M.	A.	Gunshot wound of lungs	Normal	Visible.	..	..	+	+	..	..	0.554		
H-224	59	M.	A.	Tuberculous pneumonia	Below normal.	None	..	..	+	+	..	..	0.738		
H-315	52	M.	A.	Nephritis—cerebral hemorrhage	Normal	Visible	..	..	+	..	..	..	0.738		
H-333	22	F.	A.	Puerperal endometritis	Moderately enlarged.	Visible.	..	..	+	..	..	..	0.861		
H-334	30	M.	A.	Fractured skull	Normal	Visible.	..	..	+	..	..	..	0.877	.....	Normal healthy adult.
H-307	50	M.	A.	Sudden death; cause not ascertained.	Slightly enlarged.	Visible.	..	..	+	..	..	..	0.923	.....	Dead after herniotomy.
H-328	30	M.	A.	Typhoid fever	Slightly enlarged.	Visible.	..	..	+	..	..	..	1.077		
H-303	42	F.	A.	General peritonitis	Slightly enlarged.	Visible.	+	..	+	..	..	..	0.615		
H-259	21	M.	S.	Exophthalmic goiter	Normal	Normal	+	..	+	..	..	..	0.769	0.196	

H-307.	40	M.	A.	Nephritis	Slightly enlarged.	Visible.	+	..	+	..	..	0.846	0.216	Negro.
H-244.	35	M.	A.	Morphin poisoning	Slightly enlarged.	Visible.	+	..	+	..	..	0.984		
H-297.	27	M.	A.	Hemorrhagic encephalitis(?)	Normal	Abundant.	+	..	..	..	..	1.307	.....	Negro.
H-308.	40	M.	A.	Lobar pneumonia	Normal	Normal.	+	..	..	..	..	1.461	0.310	Gland weighs 26 gms; absolutely normal in gross appearance.
H-310.	40	F.	A.	Generalized tuberculosis	Normal	Normal.	+	..	..	..	..	1.538	.....	
H-278.	18	F.	A.	?	Normal	Normal.	+	..	..	..	..	1.553	.....	Generalized skin lesions; anatomical diagnosis not made.
H-293.	28	M.	A.	Gun-shot wound of lungs	Normal	Normal.	+	..	..	..	..	1.661	0.403	Healthy young adult.
H-298.	42	F.	A.	Myocarditis	Normal	Normal.	+	..	..	..	..	1.692	0.443	Cesarean section.
H-345.	30	M.	A.	Gunshot wound of abdomen	Normal	Normal.	+	..	..	..	..	1.692	0.403	Healthy young adult.
H-358	61	M.	A.	Carcinoma of stomach	Normal	Normal.	+	..	..	..	..	1.692		
H-260.	40	M.	A.	Suppurative cholecystitis	Normal	Normal.	+	..	..	..	..	1.769	0.451	
H-246.	28	M.	A.	Liver abscess	Normal	Normal.	+	..	..	..	..	1.876		
H-287.	45	M.	A.	Aortic aneurism	Normal	Normal.	+	..	..	..	..	2.000		
H-302.	45	F	A.	Carcinoma—ovary(?)	Normal	Normal.	+	..	..	..	..	2.153		
H-347.	43	M.	A.	General peritonitis	Normal	Normal.	+	..	..	..	..	2.153		
H-312.	40	M.	A.	Fracture of skul'	Normal	Abundant.	+	..	..	..	..	2.230		
H-352.	21	M.	A.	Miliary tuberculosis	Normal	Visible.	+	..	..	..	..	2.307		
H-323.	45	M.	A.	Pernicious anemia	Small	Normal.	+	..	..	..	..	2.461		
H-283.	30	M.	A.	Endocarditis, acute	Normal	Normal.	+	..	..	..	..	2.537		
H-221.	25	M.	A.	Generalized tuberculosis	Normal	Normal.	+	..	..	..	..	2.614		
H-366.	58	M.	A.	Carcinoma of esophagus	Normal	Normal.	+	..	..	..	..	2.615		
H-286.	?	M.	A.	Apoplexy	Normal	Visible.	+	..	..	..	..	2.691		
H-278.	40	M.	A.	Aortic stenosis	Normal	Normal.	+	..	..	..	..	2.861		
H-243.	50	M.	A.	Aneurism	Normal	Abundant.	+	..	..	..	..	3.384		
H-349.	50	M.	A.	Generalized tuberculosis	Normal	Normal.	+	..	..	..	..	3.691		

* Iodin figures are in mgm.

important in the anatomical study of goiter formation, so also are the earliest deviations from the lowest iodin content compatible with normal structure. As we have just seen, the iodin content of normal glands varies within extremely wide limits, so also does the iodin content of pure colloid glands. But, on the other hand, the lowest iodin content compatible with normal structure and the highest iodin content associated with the hyperplastic changes vary within extremely narrow limits, and, further, these limits are practically the same for four out of the five animals studied. (Why the ox thyroids should show an exceptionally high lower limit of iodin compatible with normal gland structure is not clear. In an earlier paper we have suggested it might be a biological [species] characteristic, inasmuch as these animals have relatively small thyroids.) It will be recalled that in the normal glands the highest amounts of iodin observed were also quite constant, being 4.614, 4.722, 4.153, 4.768, and 3.691 mgm. per gram of dried gland, for sheep, dog, pig, ox and man respectively. This observation, when taken in connection with the quite constant lower limit of iodin necessary for the maintenance of normal structure, adds weight to the view first suggested by the iodin feeding experiments—viz., that there is a definite limit to the combining capacity of the protein for iodin, and that any excess of iodin beyond this is excreted. Such a view would accord with the fact that iodin given to animals with glands in the stage of active hyperplasia has an action like desiccated thyroid, in that it increases the nitrogenous excretion and causes loss of body weight, while iodin *not* in the form of desiccated thyroid administered to dogs with histologically normal or colloid glands does not produce these effects on metabolism.

Passing to the other degree of hyperplasia it is seen that, instead of the great drop in the iodin content noted between "normal" and "normal-early" glands, the loss of iodin, while progressive, is more gradual and reaches its lowest point in the marked glandular hyperplasia group. This is true for all animals. Of the seven cases of marked glandular hyperplasia six were from cases of exophthalmic goiter and one from a case of pernicious anemia. This is important. In the first place, it shows that in this locality the goiters of the exophthalmic group constitute the most frequent types of pure marked glandular hyperplasia, although we have frequently seen nearly as marked types of hyperplasia without the clinical complex of exophthalmic goiter. It also indicates that these forms are less frequently treated with iodin-containing compounds than are the forms occurring in childhood, puberty, pregnancy, etc.

2. The colloid series of hyperplasias (see Fig. 9 and Tables 8, 13 and 16) is in general similar to that of the normal series. We have

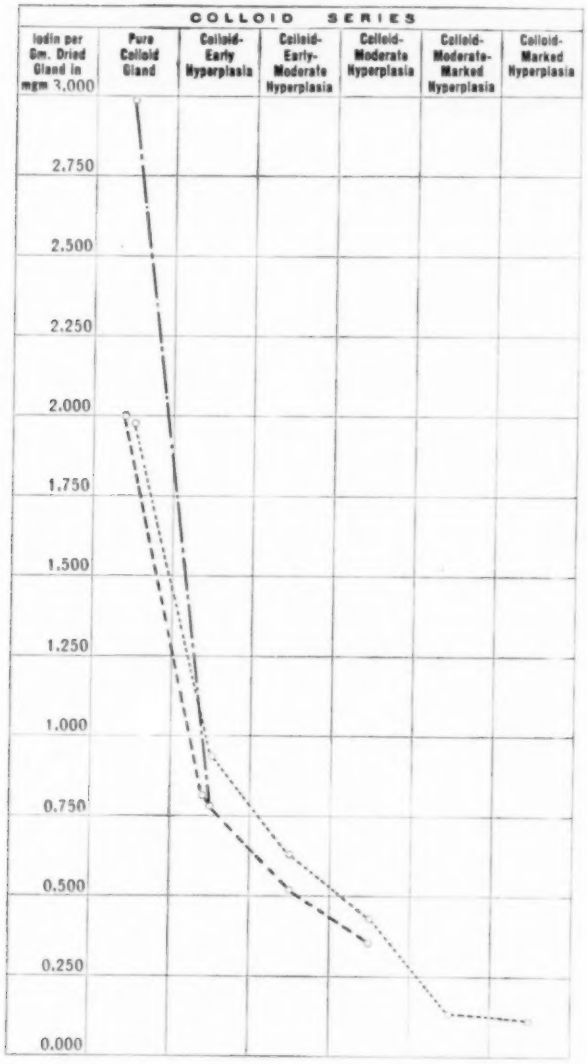


Fig. 9.—Curves compiled from the average iodin contents per gram of dried gland of the colloid series of hyperplasias in man, the dog and the pig, represented, respectively, by lines of the same character as in Figure 8.

observed the complete series in the dog. Our human series is incomplete, for the reason that complicating factors such as hemorrhages and scar formations, the result of previous hyperplasia, were present, and, having excluded such cases from the normal series, we had also to exclude them from this (colloid) series. The reason for exclusion was, in both series, the possibility of these complications modifying the findings. The general histological picture and the iodin contents of the colloid series are similar to those of the normal series. In the dog the normal and colloid series are parallel. In the human colloid series, as in the normal series, the most striking feature is the great drop in the iodin content that occurs in pure colloid glands before hyperplastic changes begin. Its physiological significance is the same and means that colloid glands are the nearest to normal that glands which have once undergone hyperplasia can become; also, that colloid glands react to the same stimuli as do normal glands. That the colloid series should show more irregularities than the normal series is to be expected. First, the size of colloid glands is more variable, as compared with the quite constant size of the normal glands; therefore, the same total amount of iodin in glands of variable size would give quite variable iodin content per gram of dried gland. Most of the large glands, however, were complicated by hemorrhage or degenerative changes and were not used. Second, the duration of the goiter, the presence of cysts, hemorrhage or degenerations, interference with the normal lymphatic drainage by pressure, fibrosis, etc., the effects of medications (*x*-ray, etc.), all modify the iodin-containing capacity of the tissue and its physiological value to the organism. In consequence of the presence of these many factors it is noteworthy that the parallelism between colloid and normal glands in the human series should be so close. In the lower animals, where many of these modifying factors are absent, a still closer parallelism exists.

COLLOID GLANDS *

There were twenty-five human glands in the colloid group. The extremes of iodin content were 3.914 and 0.784 mgm. per gram of dried gland. These extremes are somewhat greater than those of normal glands. So also colloid glands of dogs show greater extremes (3.608 and 0.846 mgm.) than the normal glands of dogs. This is to be expected, for the reason that colloid glands are of more variable size (usually larger) than are normal glands, and also for reasons indicative of a more complicated life-history, many of the factors of which are still unknown

* See tables 8 and 16.

TABLE 16.—COLLOID SERIES—MAN

Series	Sex.	Age.	Autopsy or Surgical.	Anatomical or Clinical Diagnosis.	Size of Gland.	Visible Colloid.	Colloid.	Colloid Early.	Colloid Mod.	Colloid Marked.	Perct. Water.	Iodin, per gm., Dried.	Iodin, per gm., Fresh.
												mgm.	mgm.
H-263.	M.	28	A.	Rachitic dwarf; empyema.	Moderately enlarged.	Visible.	..	..	+	....	..	0 184	
H-356.	M.	15	S.	Colloid goiter	Moderately enlarged.	Visible.	..	..	+	....	..	0.261	0.064
H-264.	F.	..	S.		Moderately enlarged.	Visible.	..	..	+	....	..	0.338	
H-369.	M.	24	S.	Exophthalmic goiter.	Moderately enlarged.	Visible.	..	..	+	....	..	0.366	
H-274.	M.	68	A.	Cerebral hemorrhage.	Moderately enlarged.	Visible.	..	..	+	....	..	0.384	
H-301.	M.	72	A.	Chronic interstitial nephritis.	Slightly enlarged.	Visible.		..	+	....	..	8.461	
H-230.	F.	78	A.	Senility; pneumonia.	Slightly enlarged.	Visible.	..	..	+	....	..	0.492	0.116
H-268.	F.	..	S.		Marked enlargement.	Visible.	..	+	+	....	..	0.446	
H-365.	F.	15	S.	Colloid goiter	Marked enlargement.	Visible.	..	+	+	....	..	0.600	
H-231.	M.	16	S.	Colloid goiter	Marked enlargement.	Visible.	..	+	..	....	..	0.595	
H-235.	F.	29	A.	Carcinoma of ovary	Moderate enlargement.	Normal.	..	+	..	....	..	0.615	
H-247.	M.	45	A.	Hemorrhage into medulla oblongata.	Normal	Normal.	..	+	..	....	..	0.769	
H-277.	F.	22	A.	Eclampsia	Moderate enlargement.	Visible.	..	+	..	....	..	0.815	
H-148.	F.	30	A.	Septicemia	Slightly enlarged.	Visible.	..	+	..	....	..	0.831	0.208
H-282.	M.	70	A.	Prostatic hypertrophy.	Slightly enlarged.	Visible.	..	+	..	....	..	0.846	
H-341.	F.	64	A.	Carcinoma of jejunum.	Moderate enlargement.	Visible.	..	+	..	....	..	0.861	
H-284.	F.	30	A.	Tuberculous peritonitis.	Moderate enlargement.	Visible.	..	+	..	....	..	0 887	
H-285.	F.	40	A.	Pulmonary embolism.	Markedly enlarged.	Abundant.	+	..	..	....	..	0.784	
H-262.	F.	32	S.	Exophthalmic goiter.		Abundant.	+	..	..	....	..	0.828	
H-266.	F.	..	S.			Abundant.	+	..	..	....	..	0.984	
H-257.	F.	40	S.	Cyst of thyroid		Abundant.	+	..	..	....	..	1.215	
H-212.	F.	23	S.	Exophthalmic goiter.		Abundant.	+	..	.	....	..	1.276	0.304
H-309.	M.	70	A.	Cerebral hemorrhage.	Small	Visible.	+	..	..	....	..	1.277	
H-317.	M.	35	A.	Generalized tuberculosis.	Slightly enlarged.	Normal.	+	..	..	....	..	1.277	
H-252.	M.	16	A.	Acute endocarditis	Marked enlargement.	Abundant.	+	..	..	....	..	1.507	
H-250.	M.	40	A.	Multiple fractures; sepsis.	Normal	Abundant.	+	..	..	....	..	1.507	0.345
H-228.	M.	35	A.	Fracture of skull	Small	Normal.	+	..	..	....	..	1.538	
H-220.	M.	35	A.	Lobar pneumonia	Normal	Normal.	+	..	.	....	..	1.540	0.331
H-326.	F.	30	A.	Cirrhosis of liver; luetic.	?	Abundant.	+	..	.	....	..	1.692	
H-330*.	F.	20	A.	Pyosalpynx; general peritonitis.	Slightly enlarged.	Normal.	+	:	..	....	..	1.769	
H-348a.	F.	..	S.	Cystic colloid goiter		Abundant.	+	..	..	....	..	1.922	
H-342.	M.	68	A.	Ulcer of stomach(?)	Small	Normal.	+	..	..	....	..	1.922	
H-233†.	M.	35	A.	Fracture of skull	Slightly enlarged.	Abundant.	+	..	..	....	..	1.922	
H-229.	F.	49	A.	Carcinoma of bladder (urinary).	Slightly enlarged.	Abundant.	+	..	..	....	..	1.970	0.614
H-314.	M.	45	A.	Pernicious anemia	Small	Normal.	+	..	..	....	..	2.307	
H-362.	M.	56	A.	Chronic interstitial nephritis.	Normal	Abundant.	+	..	..	....	..	2.615	
H-275.	M.	50	A.	Carcinoma of urinary bladder.	Moderate enlargement.	Abundant.	+	..	..	....	..	2.861	0.701
H-294.	F.	33	A.	Ectopic gestation; peritonitis.	Moderate enlargement.	Abundant.	+	..	..	....	..	2.922	
H-225.	M.	27	A.	Cardiac disease; chronic nephritis.	Slightly enlarged.	Abundant.	+	..	..	....	..	3.153	
H-245.	M.	50	A.	Carcinoma of prostate.	Normal	Normal.	+	..	..	....	..	3.507	0.798
H-299.	M.	54	A.	Chronic interstitial nephritis.	Slightly enlarged.	Abundant.	+	..	..	....	..	3.691	
H-227.	M.	40	A.	Lobar pneumonia	Slightly enlarged.	Abundant.	+	..	..	....	..	3.914	

* Negress. † Healthy young adult.

—e. g., the condition causing the hyperplasia, or the condition causing the involution (reversion). The mean and average iodin contents of colloid glands are but little below the mean and average of normal glands. This is probably accidental, for the reason that most of these cases are autopsy specimens, and many of them had received iodin medication. Reference to Table 16 shows that the iodin content of the colloid glands can be raised to the same degree as that of normal glands. It is also seen that the iodin contents of colloid glands are the nearest approach to those of normal glands that one meets, a fact which supplements their anatomical similarity to normal glands. Thus, just as in the normal series, so in the colloid series, the greatest drop in iodin content occurs between pure colloids and the first detectable hypertrophic or hyperplastic changes. With a single exception, clearly dependent on the size of the gland, the lowest iodin content associated with a pure colloid gland is above the highest iodin content associated with active hyperplasia. In the case of colloid glands one can not say at what level of iodin per gram of gland hyperplastic changes would become manifest unless it is possible to work with glands more or less constant in size and free from complications. In our series as in our dog series it has been possible to work with colloid glands but slightly different from normal glands. With such a series it is easy to prove that colloid glands are similar to normal glands as regards their iodin contents.

NORMAL-COLLOID GLANDS *

This group of eight glands has been separated for the reason that histologically we could not decide whether they were normal or colloid. If they had undergone hyperplasia it was exceedingly slight. On the other hand, the size of the glands, their stroma and the outline of the vesicles did not fit the usual picture of normal glands. The iodin content closely resembles both normal and colloid glands as regards the extremes, mean and average. Ordinarily these glands would be considered normal, and they are normal as regards any physiological or clinical significance.

RELATION OF SEX, AGE, AND SIZE OF THE GLAND TO THE IODIN CONTENT; IODIN IN THYROID TUMORS

We have not observed any difference in the iodin contents of thyroids referable to sex, either in man or in the lower animals. Slight differences in the iodin content, if present, could not be detected by the pres-

* See Table 14.

ent methods of examination, while slight differences in the weights of the glands are more easily detected.

As regards *age,* Baumann[47] was the first to report differences. Since then all subsequent observers have confirmed his general conclusions, that iodin is lowest (in some cases absent) in infants' thyroids, gradually rises during the period of growth, continues more or less constant during the middle period of life (25 to 55 years), and finally falls slightly in old age. As regards the presence of iodin in infants' thyroids, different observers have reported different results. Thus Weiss[48] reports 8 cases, the patients being from 24 days to 7½ years of age, all of which showed traces of iodin. Baumann[47] in 17 Freiburg cases, patients from 1 day to 7 years of age, found iodin present in 12. In 5 cases from Hamburg, from 5 days to 1 year of age, it was present in all. Von Rotsitzky[49] found iodin present in 6 of 8 cases, while Miwa and Stöltzner[50] found iodin in all of the 6 cases examined. Oswald[51] also reports positive findings in all his cases. Jolin[52] found iodin present in 20 of 27 cases examined. We have examined 10 subjects under one year of age and found iodin present in all. The highest was 0.482 mgm. per gram of dried gland, the lowest (an infant 1 month old) 0.027 mgm. per gram of dried gland. We have not examined any human thyroids at birth. In puppies whose mothers have been fed iodin we have detected it in glands at birth in all cases; while we have not detected any iodin in the thyroids of puppies whose mothers had not been fed iodin during pregnancy. Nagel and Roos[53] have recorded similar observations. Hunt and Seidell[54] from the results of their examinations and experiments favor the view that iodin is not uncommonly absent at birth and that the protection which such thyroids offer to mice against acetonitrile poisoning may be due to some other constituent of the protein. From the above references of recorded observations it is seen that iodin to the extent of mere traces has been found in most cases. However, findings negative to the tests at present in use, do not mean that iodin was altogether absent, and before it can be said that iodin is normally absent at birth more accurate methods of iodin determination must be devised.

47. Baumann: München. med. Wchnschr., 1896, xliii, 309.
48. Weiss: München. med. Wchnschr., 1897, xliv, 6.
49. Von Rotsitzky: Wien. klin. Wchnschr., 1897, x, 823.
50. Miwa and Stöltzner: Jahrb. f. Kinderh., 1897, xlv, 871.
51. Oswald: Ztschr. f. physiol. Chem., 1897, xxiii, 265.
52. Jolin: Festschr. f. O. Hammersten, 1906.
53. Nagel and Roos: Arch. f. Anat. u. Physiol. Supplementary Volume, 1902, p. 267.
54. Hunt and Seidell: Bull. 47, P. H. and M.-H. S., 1909, p. 49.

There is no doubt that iodin may be absent (undetectable) at birth, for the same reasons that it is in older animals (hyperplasia, cretinism).

In old age there is a slight decrease of iodin, associated with and perhaps parallel with senile atrophy. Thus, in our series, there were seven (not included in the tables) normal senile glands. The highest iodin content was 1.584 mgm., the lowest 1 mgm., and the average 1.299 mgm. per gram of dried gland, as compared with 3.691, 1.307, and 2.171 mgm. respectively for uncomplicated histologically normal glands. In conclusion it may be stated that, while age bears a quite constant relation to the iodin content, it is one of the least important factors influencing the iodin content.

The relation of the total iodin to the size of the thyroid, when taken by itself, has little value. This relationship has been the subject of many controversies between those who sought to show that iodin was related to goiter formation and those who sought to show that iodin was merely accidental. All workers have agreed that in general goiters tend to contain less iodin than normal glands. To this there are many exceptions, however. These exceptions could probably be explained, as we have previously pointed out, by comparing the histological structures with the iodin contents. We have made such comparisons in the sheep, dog and man, and have found that, as a rule, colloid goiters have more iodin (total) than have normal glands, while active hyperplasias for all the animals examined have much smaller total iodin contents than normal glands.[55] Therefore, any discussion of the relation of iodin to the size of the glands is useless unless it is based on the more important factor of histologic structure. In general it may be stated that all actively hyperplastic glands have a smaller total iodin content than normal glands; and that the total iodin varies inversely with the degree of glandular hyperplasia. On the other hand, all pure colloid glands usually have more iodin than the minimal normal content (though, as a rule, per gram of dried gland, colloid glands have less iodin than normal glands). The total amount of iodin that a gland may contain obviously depends on its size, the accidental circumstances of food, medication, locality, etc. Oswald,[56] and all subsequent observers, have shown that the colloid of colloid glands (goiters) may contain as high a percentage of iodin as the colloid of normal glands, and that such colloid has the same physiological activity as colloid from normal glands.

55. Marine and Lenhart: Further observations on the relation of iodin to the structure of the thyroid gland in the sheep, dog, hog and ox. THE ARCHIVES INT MED., 1909, iii, 66.

56. Oswald: Virchow's Arch. f. path. Anat., clxix, 444.

The presence of iodin in thyroid tumors is also of interest and may be referred to at this time. It is the rule to find iodin in fetal adenoma. We have examined nine such tumors and have found iodin in eight. The highest iodin content was 0.593 mgm. per gram of dried tumor, while the average content of the eight cases was 0.174 mgm. The specimen in which no iodin was demonstrable was removed at operation, together with some of the surrounding original thyroid tissue, which histologically was pure colloid gland (goiter) and contained 1.922 mgm. of iodin per gram of dried gland. The tumor had the usual characteristics of fetal adenoma. It was a round, encapsulated, soft, grayish, cellular mass of tissue 4 by 4 c.m., and histologically was composed of uniform, small, undistended alveoli lined with cubical epithelium. In these benign tumors the iodin content varies with the structure just as in the simple hyperplasias, being lowest in the very cellular actively growing tumors and highest in those that have undergone involution (reversion) to the colloid state. We have examined metastases from two cases of thyroid carcinoma in dogs, but found no iodin.

SUMMARY AND DISCUSSION

When all the glands are arranged according to their histological structures with normal or colloid glands at one end and the marked hyperplasias at the other, as in the full tables (Nos. 15 and 16), it is seen that the normal and colloid glands have the highest and the marked hyperplasias the lowest iodin contents. This is true for all the animals examined. It also shows that the iodin varies with the amount of stainable colloid; inversely with the size of the glands (in hyperplasias) and inversely with the degree of active hyperplasia. These relations were earlier shown to be true of dog, sheep, ox and pig thyroids. Such constant relations of iodin to the gland structure can not be accidental when taken in connection with other established facts. Thus Roos[43] has shown that the physiological action of desiccated thyroid (as ascertained by the nitrogen excretion) varies directly with the amount of iodin in organic combination. Oswald[51] repeated this work, using thyreoglobulin from normal and from goitrous glands with the same results. He also showed that the action of thyreoglobulin of goitrous glands was not different (qualitatively) from that of normal thyreoglobulin. Hunt and Seidell[54] have obtained similar results with the acetonitrile indicator. Although at first disputed, it is now abundantly confirmed that the beneficial effect, clinically, of desiccated thyroid on goiter is parallel with its iodin content. We have shown[55] that the administration of iodin to animals with active hyperplasia has the same pharmacological

effect that desiccated thyroid has on normal animals. Further, it has been shown that feeding any iodin-containing compound very quickly (in three or four weeks) causes hyperplastic glands to revert, and that this change is associated with the rapid accumulation of iodin in the gland. It is of little or no consequence whether the hyperplasia occurs in man or animals, or whether it is associated clinically with myxedema (cretinism) or with exophthalmic goiter. So also it has been pointed out that iodin prevents the occurrence of fetal thyroid hyperplasia in puppies whose mothers have had most of their thyroids removed. Also it has been shown that iodin will prevent the compensatory hyperplasia following partial removal of the thyroid. In the presence of sufficient doses of iodin all true hyperplasia is prevented. Such evidence, it seems to us, is the highest or biological proof that iodin is an active, perhaps the most active, constituent of the thyroid secretion. Recent observations by Fassin[57] and Marbé[58] indicate that iodin markedly raises the alexic (opsonic) activity of the blood serum. This is perhaps of great interest in that it may tend to explain why iodin benefits certain chronic inflammatory processes, and also why cretinoid animals manifest very low resistance to infectious agents. All of these facts show that during the active growth of the goiter there is a deficiency of iodin in the thyroid. This general observation recalls to mind the extensive chemical analyses that were made by Prevost and Maffoni,[59] by Niepce,[60] by Marchand[61] (quoted by St. Lager), and, more particularly, by Chatin,[61] and their conclusion that goiter was due to lack of iodin. They attributed the deficiency to a lack of iodin in the water and air, pointing out that along the seacoast, and in localities where iodin was present in relatively large quantities, goiter did not frequently occur. Their methods of chemical analysis were faulty, and their conclusion was easily overthrown by the extensive examinations of water, air and soil that followed. It seems now firmly established that there is an actual deficiency of iodin in the thyroid during the stage of active hyperplasia. On the other hand, the vast collections of statistical evidence on the iodin content of waters and foods, as well as the occurrence of goiter in some and not in other members of groups of men living under the same conditions of food and water, as in schools, barracks, garrisons, etc., would leave little doubt that the deficiency of iodin was not commonly due to a lack

57. Fassin: Compt. rend. Soc. de biol., Paris, 1907, lxii, 390; 1909, lxvi, 457.
58. Marbé: Compt. rend. Soc de biol., Paris, 1909, lxvi, 432.
59. Maffoni: Atti d. Accad. med.-chir. de Torina, 1846, ii, 453.
60. Niepce: Traite du goitre et du crétinisme, 1852, ii.
61. Quoted by St. Lager: Etudes sur les causes du crétinisme, Paris, 1867.

of iodin intake. Therefore, it would seem that some other agents or factors were operating in these cases. As is well known, many, indeed almost all the ordinary mineral substances, infectious agents, etc., have from time to time been accused. The infectious origin has been supported by Virchow, Bircher, Kocher, Hirsch and others, and reached its greatest popularity during the early period of bacteriological investigation (1850-85). Since Schiff, Wagner and Halsted[26] first established the fact that compensatory hyperplasia normally followed removal of the gland, and that this hyperplasia was in no way different from the changes in developing goiters, the infectious theory has been declining, while the nutritional or metabolic view has been gaining. To be sure, changing the water-supply and boiling the water have been associated with a decrease of goiter. But this could scarcely be any greater argument for an infectious origin of goiter than for a metabolic (chemical) one. But, whatever the ultimate causal factor is shown to be, it is certain that there is a deficiency of iodin in the gland, and that this deficiency of iodin in the gland is not usually due to a lack of iodin intake, but is dependent on a lack of absorption or assimilation of iodin. And it is our belief that one or more chemical substances will be found which are antagonistic to or inhibit the normal absorption or assimilation of iodin.

RELATION OF IODIN CONTENT AND HISTOLOGICAL STRUCTURE TO DISEASE PROCESSES IN GENERAL

Any discussion of the relation of the thyroid to disease processes must take account of both the histological structure and the iodin content of the thyroid, since these two factors have the following constant relation: The iodin content varies inversely with the degree of active hyperplasia. Is this relation merely accidental or is it one of cause and effect? Sufficient data are now available to prove that this relation is not accidental. These data may be summarized as follows:

1. Partial removal of the thyroid is normally followed by compensatory hyperplasia of the remaining portion. The extent of the resulting hyperplasia is known to depend on the age of the animal, the amount of gland removed and the quality of the food. Horsley,[62] Halsted,[28] Marine,[4] Marine and Williams.[4]

2. Withholding iodin increases the extent of the hyperplasia following partial removal (Marine[4]), and also causes hyperplasia without partial removal (Baumann[42, 47]).

62. Horsley: Proc. Roy. Soc., London, 1886, xl. 6.

3. The administration of iodin causes active hyperplasias of all animals to revert to the colloid state; prevents the occurrence of active hyperplasia following partial removal of glands which otherwise would undergo hyperplasia.

4. The administration of iodin prevents hyperplasia of the thyroids of puppies from bitches in which three-fourths of the gland has been removed.

5. Normal thyroids of all the animals examined have the highest and marked hyperplasias the lowest iodin contents.

6. The administration of iodin-containing compounds to the animal in any form and by any method is rapidly followed by its storage in the thyroid in quantities that bear no relation to the iodin content of the other tissues.

7. The rapidity of accumulation and the amount of iodin thus taken up by the thyroid depend on its size and the degree of active hyperplasia.

8. The physiological activity, as determined by the nitrogen excretion (Roos,[42]), by the loss of body weight (Marine and Lenhart[2],[55]), and by the acetonitrile reaction (Hunt,[44] Hunt and Seidell[54]), depends principally on the amount of iodin in organic combination.

9. It has been shown (Marine and Williams,[4] Marine and Lenhart[2], [55]) that in dog, sheep, pig, ox and human thyroids there is a quite constant minimum percentage of iodin necessary for the maintenance of normal gland structure.

While practically nothing is known of the causes leading to the iodin deficiency in the animal, the above facts, beyond doubt, show that the increased growth and divisional activity of the thyroid cells are intimately associated with a decrease of iodin, and that the increased iodin content is similarly associated with a decreased growth and divisional activity of the thyroid cells. On this basis one would expect to find thyroid changes resulting from any cause which diminished the intake or assimilation of, or increased the body demands for iodin, and that, therefore, all thyroid changes would be compensatory in nature and secondary to more fundamental causes, perhaps nutritional in nature. Also we would expect to find active hyperplasia (goiter) always preceded and accompanied by other systemic disturbances, especially those of a nutritional nature. There are other views regarding the nature of thyroid hyperplasia. Thus it is looked on by many as an infectious process in which some specific organism plays a primary rôle. The arguments for this view are of the same nature as those advanced in support of the microbic etiology of cancer. They need not be discussed here.

Another view, advanced by Gauthier[63] and Moebius,[64] is that certain types, at least, of thyroid hyperplasia are primary processes. This view is particularly applied to exophthalmic goiter, and implies that the thyroid changes are idiopathic and spontaneous, and that the thyroid abnormality by means of a hypersecretion or perverted secretion causes the disease. Without going further into the almost countless theories regarding the nature of the thyroid reaction, most of which have only an historical interest, it may be said that the three views above mentioned are the only active ones at present and may be summarized as follows: 1. Active hyperplasia is a compensatory and secondary reaction to a disturbance of nutrition. 2. It is the result of a specific infectious agent. 3. It is a primary thyroid disturbance.

A great variety of diseases are associated with or accompanied by noticeable thyroid changes. Thus rickets, lymphatism, chlorosis, cretinoid states and osteomalacia (?) are practically always associated with anatomical changes in the thyroid. Many of the prolonged infectious diseases, as lues, typhoid fever, influenza, acute articular rheumatism and tuberculosis, are frequently associated with or followed by thyroid hyperplasia. In individuals with adenoids and enlarged tonsils (lymphatism) (?), in abnormally fat children and in adiposis dolorosa,[65] the association is not infrequent. In conditions in which mental and nervous fatigue have lasted for prolonged periods of time, as in neurasthenia, and in prolonged mental states produced by worry, shock, anxiety, overwork, etc., thyroid changes are frequently observed. Also there is a particular association of thyroid changes with the systemic changes taking place at puberty; with the menstrual function; with pregnancy and lactation, and with the menopause. Lastly, thyroid changes are perhaps most frequently seen in the poorly fed and poorly nourished young (puppies, lambs, calves and children).

While all the groups of disease processes above enumerated have long been associated with thyroid changes, by some writers as cause and effect, by others as accidental, it is clear that they represent only a portion of the factors or agents capable of instituting conditions of nutrition favorable for the development of thyroid hyperplasia. Thus, while thyroid hyperplasia (goiter) may occur anywhere, it is particularly associated with certain localities. Thus far nothing specific in the geology, climate, food or otherwise has been found to account for this increased

63. Gauthier: Rev. de méd., 1890, x, 409.
64. Moebius: Centralbl. f. Nervenh., 1887, x, 225.
65. Price: Am. Jour. Med. Sc., 1909, cxxxvii, 705. Guilliam and Alquier: Arch. de méd. expér. et d'anat. path., 1906, xviii, 680.

frequency. We believe, however, that some agency or factor will be found in these districts that operates to produce hyperplasia by interference with the normal chemical processes of the body.

As was first pointed out by Hale White,[9] if one examines any large series of human thyroids he will find a considerable number showing hyperplastic changes in cases in which the subjects during life showed no symptoms known to be associated with thyroid disease. His observations have been abundantly confirmed, not only for man, but for the lower animals as well. Indeed, it is most striking in carnivora. Thus 90 per cent. of the dogs in this district have active thyroid hyperplasia, and yet, so far as we are at present able to detect clinically, most of these dogs are normal. This does not mean, however, that such animals have no symptoms directly associated or parallel with the thyroid changes. For we know that after these changes have reached a certain degree all animals show clinical manifestations. It rather indicates that the thyroid is extremely sensitive to stimuli and that the symptoms produced in most cases are below the present level of clinical detectability. In man the greater proportion of thyroids showing histological changes toward goiter formation are not associated with detectable clinical manifestations. Most of these milder degrees of thyroid changes spontaneously right themselves when the underlying or accompanying disease disappears, as, for example, the hyperplasia associated with influenza, or typhoid, or pregnancy, etc., rarely comes to clinical notice. Thus it is that all autopsy series show such a great proportion of thyroid changes without detectable clinical manifestations.

Thus far we have been discussing thyroid changes only, but it must not be overlooked that these changes are as a rule associated with other tissue reactions. The lymphoid tissues and bone marrow are very frequently hypertrophied as well. This association may be present in all the clinical forms of goiter, including cretinism. It is most frequently noticed, however, in exophthalmic goiter and in cretinism. This very common association with exophthalmic goiter was first recorded by Markham[66] and is now recognized as a constant accompanying condition in all the severe cases. There are differences of opinion as to the significance of these changes, particularly in exophthalmic goiter. Thus, Boit[67] and Capelle[68] regard the condition as lymphatism associated with exophthalmic goiter. Hansemann,[16] Hirschlaff[17] and others think that the

66. Markham: Tr. Path. Soc., London, 1858, ix, 163.
67. Boit: Frankf. Ztschr. f. Path., 1907, i, 187.
68. Capelle: Beitr. z. klin. Chir., 1908, lviii, 353.

thymic enlargement is due to thyroid toxins. Hart[69] thinks that the thymus toxins start the thyroid changes. Last, there is the view supported by Marie,[70] Hektoen,[71] Marine[4] and T. Kocher[72] and others, that these changes are a part of the disease. Whether the association is merely coincident or is dependent on some other as yet unknown nutritional disturbance is not determined. The present knowledge would indicate a very close relationship between goiter and lymphoid hyperplasia and, since lymphoid hyperplasia is also common in rickets, chlorosis and lymphatism, it would indicate that if these diseases, in common with goiter, have specific causal agents, these agents are all frequently active at the same time and in the same individual.

Finally the question arises: Are the thyroid changes associated with the diseases above enumerated identical as regards their anatomy, their chemistry and their biological reactions? So far as we are able to detect these changes, they are identical. In all there is the lowering of the iodin inversely with the degree of hyperplasia. The histological picture is identical in all, and they react alike to iodin-containing compounds. The changes in exophthalmic goiter are considered by many to be separate and distinct, and will be discussed separately.

To sum up: It is seen that active hyperplasia accompanies and follows a great variety of clinical diseases: that it is far more commonly and easily detected anatomically than clinically; that with whatever disease associated, the anatomical changes are the same; the iodin content varies in the same way in all, and they all react alike to iodin-containing compounds; that changes in the lymphoid tissues are frequently observed along with goiter, and also with other diseases with which goiter is frequently associated. On this evidence we conclude that the thyroid changes are not specific or primary, but are only the result of stimuli, constant perhaps, arising in the course of many nutritional disturbances (diseases).

RELATION OF THE IODIN CONTENT AND THE HISTOLOGICAL STRUCTURE TO EXOPHTHALMIC GOITER[73]

It is concerning the recognition and the separation of the essential from the accidental findings in exophthalmic goiter that the difficulties and controversies have arisen. This is true of both the clinical and the

69. Hart: München. med. Wchnschr., 1908, lv, 668.
70. Marie: Gaz. d. hôp., 1893, 202.
71. Hektoen: Internat. Med. Mag. Phila., 1896, iv. 584.
72. Arch. f. klin. Chir., 1908, lxxxvii, 131.
73. Dock (Jour. Am. Med. Assn., 1908, li, 1119) has lately reviewed the question of the appropriate name for this disease and we agree with him in preferring the term "exophthalmic goiter," though an objectionable one, to such designations as "Flajani's," "Parry's," "Graves'" or "Basedow's disease."

laboratory observations. The amazing quantity of literature that has accumulated about this disease in the past twenty-five years clearly indicates that neither clinical studies alone nor anatomical studies alone, nor the combination of these alone, will accurately define what should be included under the term exophthalmic goiter.

This disease is associated with and in all probability depends primarily on nutritional disturbances, the nature of which is not determined, and it is not even known whether they are fundamentally the same in all cases. The anatomical changes, the iodin relations and the general phenomena of the disease will be discussed in the order named. The views as to the relation of the anatomical changes may be grouped under three headings: (1) the view that the thyroid changes are constant and specific; (2) that the anatomical changes have no particular relationship to the disease; (3) that the anatomical changes (hyperplasia), while constantly present at some stage in all cases, are also present at some stage in all true goiters.

The view that the thyroid changes (hyperplasia) in exophthalmic goiter are constant and specific had been supported by Greenfield,[13] Farner,[23] Bramwell,[12] Hämig, [74] MacCallum,[18] Lewis,[20] Ewing,[19] Wilson[21] and others.

The view that there is no particular relationship between the anatomical changes and the disease has been supported by Virchow,[75], Renaut and Brissaud,[76] Reinbach,[77] A. Kocher[78] and many others. These are the extremes. Neither view fully accords with the facts. On the one hand, the hyperplasia is not common to this disease alone, while, on the other hand, this hyperplasia occurs at some time in all true cases of exophthalmic goiter. The explanation of the fact that one often sees colloid goiter associated with the symptom-complex of exophthalmic goiter is that the thyroid may undergo very rapid histological changes without correspondingly rapid changes in the symptoms.

Thus we have seen cases with marked hyperplasia under the influence of small doses of iodin revert to colloid goiter in from three to four weeks, while the clinical manifestations remained practically the same. As a rule, however, the symptoms become less marked as the involution (reversion) to colloid goiter occurs. Thus the histological condition of the specimen at the time of removal may be quite different from what

74. Hämig: Arch. f. klin. Chir., 1897, lv, 1.
75. Virchow: Die krankhaften Geschwülste, iii, 75.
76. Renaut and Brissaud: Semaine méd., 1895, No. 39.
77. Reinbach: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1901, viii, 247.
78. Kocher, A.: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1902, ix, 1.

it would have been even two weeks before. Similar histological changes to those in exophthalmic goiter are also seen in all developing functional hyperplasias of man and animals. There are differences of degree and differences depending on the age of the animal, the number of times the gland has reverted and undergone hyperplasia, the presence of complications, etc., as outlined above. The reaction with iodin is the same in all forms of functional hyperplasia. The marked hyperplasias of exophthalmic goiter react exactly in the same way as do the hyperplasias in animals or the hyperplasias of childhood, puberty and pregnancy in man.

In the light of these facts the third view—viz., that active hyperplasia is of constant occurrence at *some* phase in all true cases of exophthalmic goiter but that similar changes occur in *all* developing goiters—is the one most likely to accord with all the facts.

Of 26 cases clinically diagnosed as exophthalmic goiter in which the patients were operated on by Dr. G. W. Crile at Lakeside Hospital 15 had active hyperplasia, varying from colloid-early to marked glandular hyperplasia. Eight had pure colloid goiters. Two had pure colloid goiters containing actively growing fetal adenomata and one had a normal thyroid as regards size, histology and iodin content. With this series one would be inclined to agree with Virchow[74] when he wrote that the phenomena of exophthalmic goiter depended on neither a distinct variety of goiter, nor a distinct size, nor yet a distinct stage of thyroid change, did we not further inquire into the cases. It was found that the patients with pure colloid goiter had been treated with iodin-containing substances shortly before operation. These cases clinically were quite typical cases of exophthalmic goiter. This finding bears out the observations reported from most of the large clinics that one frequently sees cases of exophthalmic goiter with colloid glands. This, however, means that the thyroid reacts too quickly (three to four weeks) for the clinical manifestations to follow and not that in the progressive stage of the disease there was no active hyperplasia, for we now know that all colloid goiters have been preceded by active hyperplasia. We also know that the histological appearance of the thyroid may change from week to week and there can be little doubt that the varied histological findings reported by all observers is due merely to the stage of the process (regressive or progressive) at the time of the operation. The case in which the thyroid was normal is not unique. There are several reports of such cases. These cases must either be considered errors in diagnosis or that the manifestations were too recent for cell reactions to occur. We are inclined to consider such cases not true exophthalmic

goiter, but rather as severe cases of some clinically closely allied disease like neurasthenia or psychasthenia.

Thus, after carefully reviewing the data, we conclude that thyroid hyperplasia is of constant occurrence at some stage of the disease, but that it also occurs in all developing goiters in all animals.

RELATION OF THE IODIN CONTENT OF THE THYROID TO EXOPHTHALMIC GOITER

The iodin varies inversely with the degree of hyperplasia. We have just seen that the histological structure of the goiters as we obtain them is quite variable; so also is their iodin content. But, just as there is a constant histological change (active hyperplasia) at some phase in all true cases of exophthalmic goiter, so there is a uniform lessening of the iodin content corresponding with the increasing degree of hyperplasia. Oswald[79] in general found the percentage of iodin lowered in exophthalmic goiter, but he also observed cases in which it was increased. Caro[80] in a single severe case found the iodin very high. Reinbach[81] could make out no relation between the amount of colloid and the amount of iodin. Kocher[82] found exophthalmic goiter glands always lower in iodin than normal glands, even to one-thirtieth of the normal.

Two conditions must be fulfilled before one can conclude that iodin bears no relation to exophthalmic goiter: (1) a large series of cases, (2) careful histological comparisons. It seems that this may account for many of the reports in which no relation could be made out, just as it explains why constant anatomical changes were not established earlier. The histology and iodin content for human goiter are modified by so many factors that it is necessary to examine a large series in order to include and allow for variations dependent on the food, medication, age, stage of the disease, etc.

In our 26 cases there was no case in which the iodin did not vary inversely with the histological structure. It was highest in the colloid glands, lowest in the marked hyperplasias, and the highest iodin content associated with hyperplasia was always below the lowest associated with pure colloid gland. We can conclude, therefore, that the iodin content in exophthalmic goiter always varies inversely with the degree of hyperplasia just as in all other forms of active hyperplasia. There are the same difficulties in the interpretation of the anatomical changes. These

79. Oswald: Virchow's Arch. f. path. Anat., 1902, clxix, 444.
80. Caro: Berl. klin. Wchnschr., 1907, xliv, 519.
81. Reinbach: Centralbl. f. Chir., 1898, xxv, 545.
82. Kocher: Arch. f. klin. Chir., 1901, lxiv, 454.

can only be avoided by working with large series and by carefully comparing the iodin content with the histology.

The severity of the cases in general varies with the degree of thyroid and lymphoid hyperplasia. Autopsy and surgical reports from all sources have shown this. In our series there were six patients with marked glandular hyperplasia, of whom four died. Of the four that died three had slight manifestations suggestive of supervening myxedema (dry skin, pigmentation, loss of pubic, axillary and scalp hair, etc.). The ten patients with colloid goiter recovered.

As to the cause of death after operation in these severe cases there are three views: (1) that it is due to the poisoning of the tissues with an excess of thyroid secretion; (2) that it is due to the lymphoid hyperplasia (status lymphaticus); (3) that it is due to true exhaustion of all the tissues, particularly the central nervous system.

The first view embodies the well-known theory of Moebius and Gauthier[63] on which the surgical, the cytotoxic and serum treatments rest. Are these hyperplastic glands secreting an increased quantity of physiologically active secretion? If such were the case, the same changes should be produced in the thyroids of animals by feeding with hyperplastic glands as by feeding with normal or colloid glands. This, as is well known, is not true. The physiological activity of such thyroids, as determined by the nitrogen excretion and the histological changes produced in dogs' thyroids, depends on the amount of iodin they contain and the iodin varies inversely with the degree of thyroid hyperplasia. Also, the fact that desiccated sheeps' thyroid in large doses (2 to 5 grams daily) usually increases the clinical symptoms in proportion to the severity of the case can not be interpreted as proof of physiological hypersecretion, for the reason that the effect of such desiccated thyroid on these patients depends on the quantity of iodin it contains. That this is true can be easily shown by the fact that iodin administered to these cases has (so far as we are able to estimate) the same action as desiccated thyroid. In individuals with normal glands just the opposite of this is true. Iodin in similar doses has no noticeable effect, while desiccated thyroid produces the same manifestations of physiological activity as are shown in cases of exophthalmic goiter, and, also, just as in the exophthalmic goiter cases, the physiological activity depends on the amount of iodin in organic combination. The results of operative treatment according to the hypersecretion theory should be most favorable in those cases with the most active hyperplasia. As a matter of fact, the opposite is true—viz., that the operative mortality is greatest in those cases with the most marked hyperplasia and the lowest iodin contents.

The clinical severity as determined by the symptoms is uncertain, for the reason that the gland may revert to the colloid state with the apparent preservation of the original symptoms. In such cases, as in the cases with slight hyperplasia, the mortality from operation is very low. And, therefore, the mortality, as based on the number of cases clinically diagnosed as exophthalmic goiter, is of little importance. Another view that squeezing or manipulation of the gland produces the marked rise in pulse rate and temperature (so-called hyperthyroidism) by overloading the circulation with the "toxic" secretion has been proved untrue, for the reason that operations elsewhere on the body or injuries, or even mental shock, in this class of cases are with proportionate frequency followed by these symptoms.

The second view that the lymphoid hyperplasia (status lymphaticus) is the determining cause of death in these cases has lately been revived and reviewed by Capelle.[83] The presence of lymphoid hyperplasia in these severe cases of exophthalmic goiter was perhaps first described by Markham[66] and later by Marie,[70] Hektoen,[71] Hansemann[16] and many others. Capelle has found in the collected reports that 44 per cent. of the exophthalmic goiter patients dying of some intercurrent disease; 82 per cent. of those dying directly of the disease and 95 per cent. of those dying after operation had persistent thymus. From these data he concludes that this lymphoid hyperplasia is a separate and complicating condition in exophthalmic goiter. Others look on these changes as part of the essential anatomical lesions in all severe cases. The fact that these same changes are also present in cretin lambs, dogs and children, and also in many cases of adult myxedema, compels us to conclude that it is merely a part of the systemic reaction to the cause or causes producing goiter. We fully agree with Capelle that in all severe cases of exophthalmic goiter there is lymphoid hyperplasia, and also that the mortality is greatest in those cases, but we can not accept his conclusion that the mortality depends on the presence of lymphoid hyperplasia alone. We consider both the thyroid and lymphoid changes as common and the truest indices of the severity of the disease.

The third view is that death is due to exhaustion. This view, it seems to us, more nearly accords with the observed phenomena. All observations go to show that the gland is hyperactive, but that this activity is compensatory in nature. So also all the facts indicate that the quantity of the secretion is increased, but that its physiological activity is decreased. The frequency with which myxedema follows exoph-

83. Capelle: Beitr. z. klin. Chir., 1908, lviii, 353; München. med. Wchnschr., 1908, lv, 1826.

thalmic goiter can not be explained as accidental and, as has been suggested by several authors, is perhaps the greatest objection to the hypersecretion theory. In endemic cretinism, in both man and animals, one notes the same kind of anatomical changes as are observed in exophthalmic goiter, and, as already stated, these changes are common to all developing functional hyperplasias of the thyroid. This is, however, only the anatomical verification of the old clinical phrase that endemic goiter is the first stage of the process leading to cretinism and it seems to us, as Ord[3], [24] has pointed out, that in myxedema following exophthalmic goiter, we have a very close analogy with cretinism. In this connection it is of great interest to note that Horsley[62] in his experimental myxedema in monkeys has described a nervous stage followed by the dull listless stage so characteristic of fully developed myxedema, and also that McGarrison,[36] in his excellent clinical report on cretinism in the Himalayas, has very carefully described this nervous stage. Whether these anatomical and clinical similarities between the life-history of exophthalmic goiter and of cretinism are closely related or are merely accidental is a problem that is worth very careful study. The nervous symptoms are, however, not common to this disease alone, but may be present in varying degrees in a variety of nervous and mental diseases in individuals with histologically normal thyroids, as in neurasthenia and psychasthenia. The same may be said of the symptoms of extreme tachycardia and high temperature which so frequently follow operations, injuries or mental shocks in these cases. The same phenomena are observed in heat exhaustion. The onset of the disease, while it may be quite sudden, is almost always progressive and preceded by some chronic debilitating disease as typhoid fever, influenza, or by severe mental strain as overwork, anxiety, etc. The whole clinical picture, it seems to us, is one of exhaustion, the seat of which is particularly the central nervous system. Certainly the nervous manifestations predominate and perhaps cloud (at least, by our present standards of interpretation) the true picture of exhaustion. It is difficult to understand why partial removal is so quickly followed by a further hyperplasia of the remaining portion which differs anatomically from the first portion removed in no essential way, and why in spontaneous recovery the gland always returns to the colloid state, unless we assume that the process of hyperplasia of the thyroid is a compensatory one..

In the light of our present knowledge of the anatomy, the chemistry and the biology of thyroid hyperplasia we can not conclude that the thyroid changes in exophthalmic goiter are either primary or specific or that such thyroids are producing an increased amount of a physio-

logically active secretion. On the other hand, we believe that the thyroid changes in exophthalmic goiter are always compensatory or secondary to some more fundamental cause or causes and that there is a hypersecretion quantitatively but a hyposecretion qualitatively (physiologically), and, lastly, that the usual final stage of all cases unless terminated by death or relative recovery is myxedema.

RELATION OF THYROID CHANGES AND IODIN CONTENT TO CRETINISM AND MYXEDEMA

It is now generally accepted that the major disturbance in sporadic and endemic cretinism, in operative myxedema (cachexia strumipriva), and in natural myxedema (Gull's disease) is a lack of thyroid function. This opinion is largely the result of the clinical and anatomical observations from many sources, among which may be mentioned the work of Gull,[83] Kocher,[84] Ord,[85] Hun and Prudden,[25] Virchow[86] and Osler[87]; of the experimental observations of Kocher,[88] Reverdin,[89] Stokes,[90] Gordon,[91] Horsley[92] and Halsted[93]; of the therapeutic studies by Murray,[94] Mackenzie[95] and von Bruns.[96]

So, also, through the work of St. Lager,[97] Niepce,[98] Morel,[99] Hirsch (loc. cit.), McGarrison[35] and others, it has been shown that 75 per cent. of all cretins have enlargement of the thyroid clinically, and also that the general relation of goiter to cretinism may be summed up in the words of Morel, that "goiter is the first stage on the road leading to cretinism." From the above generalizations it can be seen that the terms "cretinism" and "myxedema" do not represent simple clinical, anatomical or physiological conditions, but must include all the gradations of the processes of which clinical cretinism and myxedema are the terminal

84. Kocher: Deutsch. Ztschr. f. Chir., 1892, xxxiv, 556.
85. Ord: Brit. Med. Jour., 1888, i, 1162.
86. Virchow: Die krankhaften Geschwülste, 1863; Berl. klin. Wchnschr., 1887, xxiv, 121.
87. Osler: Tr. Cong. Am. Phys. and Surg., 1897, iv, 169.
88. Kocher: Arch. f. klin. Chir., 1883, xxix, 254.
89. Reverdin: Rev. méd. de la Suisse rom., 1882, 539.
90. Stokes: Brit. Med. Jour., 1886, ii, 709.
91. Gordon: Lancet, London, 1886, ii, 65.
92. Horsley: Lancet, London, 1884, ii, 1133.
93. Halsted: Jour. Exper. Med., 1909, xi, 175.
94. Murray: Lancet, London, 1893, i, 1130.
95. Mackenzie: Lancet, London, 1893, i, 123.
96. Von Bruns: Beitr. z. klin. Chir., 1896, xvi, 521; 1894, xii, 847.
97. St. Lager: Etudes sur les causes du crétinisme, etc., Paris, 1867.
98. Niepce: Traite du goitre et du crétinisme. Paris, 1851, i.
99. Morel: Du goitre et du crétinisme, etc. Paris, 1864.

stages. The intermediate stages are best indicated by the various degrees of active thyroid hyperplasia and in an earlier paper one of us (Marine[4]) suggested the borrowed term "cretinoid" (Gull[23]) as the best descriptive word for the several degrees of hyperplasia seen in dogs, sheep, ox, pig, and human thyroids, since the greater number of these animals having active hyperplasia have no detectable clinical manifestations.

The anatomical changes usually present in typical cretin animals are characterized by the extensive overgrowth of fibrous tissue resulting from the dying off of the epithelial cells. We have not found any definite anatomical descriptions of glands in the early stages of this fibrous tissue replacement of the epithelial hyperplasia. It has been our fortune to observe five cretin puppies and two cretin lambs in which these changes were occurring. As previously mentioned (under anatomical descriptions), the epithelial cells at first enlarge and the nuclei become hyperchromatic. Later these cells become irregular in size and shape and the normally regular outline of the vesicular epithelium is broken. The increased connective tissue crowds out these degenerated cells and finally the vesicle, much reduced in size, becomes filled with the irregular cell masses and the detritus of the more degenerated cells. These changes have been observed only in thyroids of lower animals with clinical manifestations of cretinism. Of perhaps greater interest is the fact that similar disturbances in the nucleus-plasma relations of the epithelial cells have been observed in four cases of exophthalmic goiter which clinically showed manifestations of myxedema.

When these anatomical changes and their clinical associations with cretinism and myxedema are considered together they suggest that the further ability of the cells to grow and divide normally has been seriously disturbed and that the major factors in this disturbance are overwork and lack of proper nutrition, as was pointed out by Popoff[100] for protozoan cells. In cretin puppies we have been able, by the administration of iodin, to make these cells revert to the flattened cubical form, while the gland as a whole returned to the colloid or resting condition, and later by partial removal to produce a perfectly regular and uniform hyperplasia in the same gland. Professor Howard and Dr. Schultz, to whom we have referred these observations, are of the opinion that these thyroid changes, consisting in the production of depression and the recovery therefrom, are comparable to the protozoan cell changes described by Hertwig and his pupils. The most suggestive explanation at present seems to be that these degenerative and atrophic cell changes are the

100. Popoff: Arch. f. Protistenk. (Suppl.) Festband f. R. Hertwig, 1907, p. 43.

result of prolonged and unrelieved physiological stimulation to meet some deficiency, and that cretinism and myxedema are the final stages of the failure in compensation.

In view of what has been said above, the earlier statement that in cretinism and myxedema there is a lack of thyroid function is somewhat misleading because the thyroid in the early stages of the process is hyperactive, while, at the same time, the body as a whole suffers from a lack of normal function. Thus it would appear that in the cretinoid and in the myxedematous process the real deficiency lies in the physiological value of the thyroid secretion to the organism. This deficiency may be produced either by atrophy or absence of the gland, or by the absence of the normal elements of nutrition with which the normal metabolic activities of the gland are concerned. Iodin is perhaps one of these elementary deficiencies.

In the true cretin the gland histologically presents marked overgrowth of fibrous tissue, with a corresponding disappearance of the epithelial elements, while in the preclinical stage the gland presents a marked epithelial hyperplasia with relatively slight increase in the supporting fibrous tissue. Thus with the progressive epithelial hyperplasia finally giving way to the fibrous overgrowth as typifying the anatomical changes in the cretin or myxedema thyroid, it may be said that the symptom-complex varies with the degree of epithelial hyperplasia and fibrotic atrophy.

As regards the iodin content in human cretin thyroids no specific observations are recorded. In the five cretin dogs examined by us we could find no trace of iodin, and in the four cases of exophthalmic goiter showing clinical signs of myxedema the highest iodin content was 0.544 and the lowest 0.118 mgm. per gram of dried gland. This suggests that the iodin content varies inversely with the degree of hyperplasia and fibrosis in both cretin and myxedema glands. With the exception of tumors and infants' thyroids, these were the lowest iodin contents observed. There are variations and modifications in the iodin content and histologic structure of cretin and myxedema glands in man that are comparable to the variations above noted in other clinical varieties of goiter, and depend on the age of the individual, previous medication, the presence of complicating and degenerative changes, etc. These variations and modifications we believe could be easily explained if the life-history of such patients could be accurately ascertained. But, as this at present is quite impossible, our hope lies in the accumulation of sufficient cases to include all the variations and the essential types of change as well.

In conclusion we believe that the various degrees of thyroid hyperplasia are but stages in a common process the final result of which is cretinism or myxedema and that the percentage of iodin varies inversely with the degree of hyperplasia and fibrosis.

CONCLUSIONS

1. Active thyroid hyperplasia is present in all developing goiters in all animals.

2. All thyroid hyperplasia, so far as we can determine, is anatomically, chemically (iodin) and biologically the same.

3. Thyroid hyperplasia develops in both normal and colloid glands.

4. Colloid glands, anatomically, chemically and biologically, are the nearest approach to the normal gland that hyperplasias can become and obey all the known biological laws of normal glands in so far as these laws are at present known.

6. The various degenerations, hemorrhages and cysts are secondary and complicating changes engrafted on to the three fundamental types of normal, hyperplastic and colloid glands.

7. Iodin is necessary for normal thyroid activity.

8. The iodin content varies inversely with the degree of hyperplasia.

9. The percentage of iodin present in thyroids is variable, but there is a quite constant minimum percentage necessary for the maintenance of normal or colloid gland structure.

10. Iodin is taken up rapidly by the thyroid, the rapidity depending on the degree of active hyperplasia.

11. Mild degrees of thyroid hyperplasia accompany or follow many of the chronic nutritional disturbances without detectable clinical symptoms referable to the thyroid.

12. Exophthalmic goiter is constantly accompanied during the progressive stage of the disease by thyroid hyperplasia and the iodin percentage varies inversely with the degree of hyperplasia.

13. In endemic cretinism the fibrous overgrowth with atrophy of the gland cells is consequent on active hyperplasia and is associated with a very low iodin content.

14. In myxedema the anatomical and iodin changes are similar to those of cretinism.

We wish to acknowledge our indebtedness to Prof. W. T. Howard for the anatomical material; to Prof. G. W. Crile for his surgical material at Lakeside Hospital, and also to thank Professors Howard and G. N. Stewart for their careful criticisms and suggestions.

THE USE OF ACTIVE AND INACTIVE SERUM IN THE COMPLEMENT DEVIATION TEST FOR SYPHILIS *

HOMER F. SWIFT, M.D.

Attending Physician, Department of Dermatology, New York University and Bellevue Hospital Medical College

NEW YORK

In a recent communication[1] I presented a comparative study of the value of the Wassermann and Noguchi methods for the serum diagnosis of syphilis. The latter was shown to be more sensitive in syphilis, but sera from seventeen non-syphilitic patients were positive with this method and negative with the Wassermann. Attention was called to the fact that eight of the non-specific reactions became negative when inactive serum was substituted for active. The question then arose: Does inactivating destroy the value of the method with syphilitic sera? The present communication is a report of the work done to determine this point.

The simplicity of the Noguchi technic[2] makes it the most desirable method for general use, if it can be so modified that it is as reliable as the original Wassermann procedure. The principle of the two methods is the same; that is, the suspected serum, the complement and antigen, all from different sources, are first incubated to bind complement, and this binding is later detected by the absence of hemolysis. The difference is that with Noguchi's method human erythrocytes are used instead of red blood cells from sheep, and the human serum is not inactivated. This latter appears to me a most important point, but there is comparatively little experimental evidence concerning it.

Sachs, last year, in a brief report,[3] called attention to the fact that active sera give stronger reactions than inactive, but that unheated sera obtained from non-syphilitic patients sometimes give a positive reaction. He showed that adding an alkali to a positive serum causes it to lose its

---

* From the Pathological Department of the New York University and Bellevue Hospital Medical College. Aided by a grant from the Committee on Scientific Research of the American Medical Association.

1. Swift, H. F.: Tr. Assn. Am. Phys., 1909; id., THE ARCHIVES INT. MED., iv, 376.

2. Noguchi, H.: Jour. Exper. Med., 1909, xi, 392.

3. Sachs, H.: Verhandl. d. deutsch. dermat. Gesellsch., 1908, x, 167.

complement-binding power, and that acidifying a negative-reacting syphilitic serum with hydrochloric acid causes it to react positively. In a later paper[4] he demonstrates that inactivating a syphilitic serum causes it to lose the power of precipitating the globulins with distilled water (Klausner's reaction[5]), but that the precipitate will form if hydrochloric acid is added to the inactive serum. He also proves that heating a serum to 62 C. produces such a change that it entirely loses its complement-binding power. Gross and Volk[6] demonstrate that a similar heating prevents the formation of a precipitate when the serum is mixed with lecithin as in Porges' test.[7] The effect of heating to 62 C. apparently is to increase considerably the alkalinity of the serum, thereby producing such a change in the albuminoid that it will no longer react with the lipoid to bind complement.

Sachs suggested that a comparative study be made with active and inactive serum and Boas[8] followed this suggestion. Using decreasing quantities of suspected serum, in amounts of 0.2, 0.1, 0.05, 0.025, and 0.001 cubic centimeters against 0.1 cubic centimeter of guinea-pig serum, he shows that from one-half to one-fourth the amount of active serum is required to produce the same degree of inhibition as inactive serum. He also demonstrates that the reaction appears earlier in the primary stage and persists longer, under treatment, when unheated serum is used. On the other hand, he presents a table of forty-five different sera from non-syphilitic patients which gave a positive reaction when 0.2 cubic centimeter of unheated serum was employed. All of these sera gave no reaction when they were inactivated. He calls attention to the fact that ox, horse, sheep and rabbit sera are often anticomplementary when used in the fresh state, and concludes that it is not safe to use active serum, and that any method in which it is employed is unreliable.

The results of Boas' observation can not, however, be strictly applied to the Noguchi method, for there is a striking difference in the ratio between the amount of serum, human and guinea-pig respectively, used in the two methods. In Boas's experiments 0.2 cubic centimeter of human serum was used against 0.1 cubic centimeter of guinea-pig serum, the ratio being two to one; while with the Noguchi method[2] one drop from a capillary pipette, or 0.02 cubic centimeter, is used, against

4. Sachs, H.: Semaine méd., 1908, xxviii, 301.
5. Klausner, E.: Wien. klin. Wchnschr., 1908, xxi, 214.
6. Cited by Toyosumi, H.: Wien. klin. Wchnschr., 1908, xxi, 611.
7. Porges, O.: Wien. klin. Wchnschr., 1908, xxi, 206.
8. Boas, H.: Berl. klin. Wchnschr., 1909, xlvi, 400.

0.04 cubic centimeter of guinea-pig serum; the ratio being reversed; that is, one to two. Even with this small proportion of active serum I have obtained a number of positive reactions with non-syphilitic sera.

METHOD

Throughout this study the results obtained by the Noguchi method and its modification have been controlled by the Wassermann method. In the latter the quantity of all the reagents has been reduced one-half, but the proportion was the same as originally described. An alcoholic extract of syphilitic liver made after the formula of Michaelis and Lesser[9] has been employed as antigen. In the Noguchi modification parallel tests have been carried out with both active and inactive serum. With the active serum one drop from a capillary pipette as described by Noguchi has been used; while with the inactive serum the amount has been 0.08 cubic centimeter. Here the proportion of human to guinea-pig serum is two to one, the same as in the Wassermann method. As antigen, the same alcoholic extract has been used in all the methods, and in the same proportion. Double the amount of antigen did not inhibit hemolysis when used without the addition of human serum; hence the possibility of the antigen being too strong was eliminated. As the slips of paper impregnated with antigen have not proved stable in my hands, the antigen was kept in solution, and a fresh emulsion with normal saline prepared each day. Fresh guinea-pig serum was used as complement. The human red blood cell emulsion was prepared throughout the series from blood from the same person. The anti-human amboceptor, dried on paper, was kindly furnished by Dr. Noguchi. The incubation time corresponded in all the tests, and the various tests with corresponding sera were made on the same day with the same complement, so that conditions as nearly uniform as possible prevailed.

RESULTS

A. With Syphilitic Sera.—The results obtained with sera from syphilitic patients are given in Table 1. The classification is based on the stages and manifestations of the disease with farther subdivision according to the degree of treatment. The intensity of the reaction is indicated by signs: ++ indicating complete inhibition; + marked; $\pm$ slight but distinct inhibition; and — complete hemolysis. Noguchi[10] attaches great importance to the various grades of reaction. He regards complete and

9. Michaelis, L., and Lesser, F.: Berl. klin. Wchnschr., 1908, xlv, 301.
10. Personal communication.

TABLE 1.—COMPARISON OF THE WASSERMANN AND THE NOGUCHI METHODS WITH ACTIVE AND INACTIVE SERUM

Treatment.	None.												Slight.												Fair.												Good.											
Method	Wass.				Nog. Act.				Nog. Inact.				Wass.				Nog. Act.				Nog. Inact.				Wass.				Nog. Act.				Nog. Inact.				Wass.				eg. Act.				Nog. Inact.			
Degree of reaction	++	+	±	–	++	+	±	–	++	+	±	–	++	+	±	–	++	+	±	–	++	+	±	–	++	+	±	–	++	+	±	–	++	+	±	–	++	+	±	–	++	+	±	–	++	+	±	–
Stage																																																
Primary	4	2	0	1	4	2	0	1	4	2	0	1																																				
Secondary	10	1	0	1	12	0	0	0	10	2	0	0	22	4	0	0	22	2	2	0	21	5	0	0																								
Tertiary	5	0	1	0	6	0	0	0	5	0	1	0	8	0	0	0	6	1	1	0	6	2	0	0	4	1	2	0	4	1	2	0	4	1	2	0	1	0	3	0	2	0	2	0	1	1	2	0
Latent, (early)	0	1	0	0	0	1	0	0	0	1	0	0	7	1	2	2	10	1	0	1	7	2	2	1	7	5	4	3	9	5	2	3	7	6	3	3	1	0	0	0	1	0	0	0	1	0	0	0
Latent, (late)	0	0	0	1	0	0	1	0	0	0	0	1	3	0	0	0	3	0	0	0	3	0	0	0	2	1	6	1	6	1	2	1	3	2	3	2	3	0	5	4	4	3	1	4	3	1	4	4
Syphilis of nervous system	5	1	3	0	6	2	1	0	6	0	3	0	1	2	0	0	2	1	0	0	2	1	0	0	1	2	2	2	3	2	1	1	1	3	1	2	0	0	2	2	0	0	1	3	0	0	2	2
Visceral	4	0	0	1	3	1	0	1	3	1	0	1													1	0	1	0	2	0	0	0	1	0	1	0												
Tabes	2	2	1	3	1	4	0	3	1	2	2	3	1	1	0	2	2	1	0	1	1	1	0	2	0	1	1	1	1	1	1	0	0	1	2	0	0	1	2	0	1	1	1	0	0	2	1	0

marked inhibition as diagnostic and slight inhibition as only prognostic. He asserts that if the latter degree of reaction is obtained in known syphilis treatment should be continued. Regardless of treatment the results in Table 1 may be summarized as in Table 2.

In primary syphilis the figures correspond; in the secondary and tertiary stages of the disease, with skin or mucous membrane manifestations, a positive reaction was obtained with every test, except one with the Wassermann. In the second stage the Noguchi method with active serum gave a weak reaction twice. This was apparently due to the summation of human and guinea-pig complement being too much to absorb completely, for when the human complement was destroyed by heat the reactions became strongly positive. In the latent stage and in internal man-

TABLE 2.—SUMMARY OF TABLE 1. PERCENTAGE OF POSITIVE RESULTS

Stage of Syphilis.	No. of Cases.	—Wassermann—			–Noguchi (Active)–			Noguchi (Inactive)		
		Diagnostic %	Prognostic %	Total %	Diagnostic %	Prognostic %	Total %	Diagnostic %	Prognostic %	Total %
Primary	7	86	0	86	86	0	86	86	0	86
Secondary	38	97	0	97	95	5	100	100	0	100
Tertiary	25	76	24	100	84	16	100	80	20	100
Latent (early)....	33	66	18	84	80	6	86	70	14	84
Latent (late)	26	35	42	77	66	15	81	46	27	71
Nervous	23	52	30	82	70	14	84	55	27	82
Visceral	7	72	14	86	86	0	86	72	14	86
Tabes	18	44	22	66	66	11	77	44	28	72

ifestations of the disease the Noguchi method with active serum gave the largest number of diagnostic reactions; the same method, with inactive serum, gave the next greatest number, and the Wassermann method, the fewest. The total number of reactions nearly corresponds in all the methods, but the advantage in diagnostic results is with the Noguchi method, using active serum.

In a few tests with the Wassermann reaction active serum was used. In fifteen, 0.1 cubic centimeter of serum was used against 0.05 cubic centimeter of complement; eleven of these corresponded with the Noguchi method (active serum); two were stronger and two were weaker. Sixteen were tried with 0.025 cubic centimeter of human serum, and the reactions agreed in both methods. Here the proportion of serum to complement corresponded in both.

B. With Non-Syphilitic Sera.—Eighty-five sera were obtained from patients in whom the possibility of syphilis could be fairly well excluded. Of these, sixty-five were negative with all the methods. Twenty gave a reaction with the Noguchi method with active serum; of this number fifteen were so-called diagnostic reactions and five prognostic (see Table 3). All of the twenty were negative with the Wassermann reaction, and also with the Noguchi method, when inactive serum was substituted in the

TABLE 3.—EFFECT OF INACTIVATION ON ANTICOMPLEMENTARY SUBSTANCE IN NON-SYPHILITIC SERA.

Diagnosis.	—Wassermann Method.—				——Noguchi Method.——			
	Inactive.		Active.		Inactive.		Active.	
	Amt. of Serum. c.c.	Reaction.	Amt. of Serum. c.c.	Reaction.	Amt. of Serum. c.c.	Reaction.	Amt. of Serum. Drops.	Reaction.
Herpes progenitalis ...	0.1	—	0.1	++	0.08	—	1	+
Carcinoma of penis....	0.1	—	0.1	+	0.08	—	1	+
Leprosy	0.1	—	0.1	+	0.08	—	1	+
Pyogenic Dermatitis ..	0.1	—	0.1	+	0.08	—	1	+
Erythromelalgia	0.1	—	0.1	+	0.08	—	1	+
Epilepsy	0.1	—	0.1	+	0.08	—	1	+
Nephritis	0.1	—	0.1	++	0.08	—	1	++
Traumatic arthritis ...	0.1	—	0.1	+	0.08	—	1	+
Monoplegia	0.1	—	0.1	++	0.08	—	1	+
Chancroid	0.1	—	0.025	+	0.08	—	1	+
Ulcerative proctitis ...	0.1	—	0.025	+	0.08	—	1	+
Rosacea	0.1	—	0.025	+	0.08	—	1	+
Anemia, pernicious ...	0.1	—	0.025	+	0.08	—	1	+
Multiple sclerosis	0.1	—	.....	.....	0.08	—	1	+
Malaria	0.1	—	.....	.....	0.08	—	1	++
Carcinoma of uterus...	0.1	—	0.1	—	0.08	—	1	+
Carcinoma of uterus two cases.	0.1	—	0.1	+	0.08	—	1	+
Chancroid	0.1	—	.....	.....	0.08	—	1	+
Scleroderma	0.1	—	.....	.....	0.08	—	1	+

quantity of 0.08 cubic centimeter. This would indicate that inactivation destroys the substance which causes the non-specific reaction, and, with the determination of this point in mind, active serum was used in the Wassermann reaction (see Table 3). In twelve of the tests 0.1 cubic centimeter of serum was used and in four 0.025 cubic centimeter, but in most the results agreed when active serum was employed in either method. The table demonstrates definitely that non-syphilitic sera which

give the reaction in the active state lose this property when the serum is heated to 56 C. for one-half hour.

It is a matter of considerable interest that non-syphilitic sera, when kept for several days in the ice-chest, often become strongly anticomplementary, but when again inactivated lose this property; hence old controls should always be reinactivated on the day they are to be used in a test.

EFFECT OF INACTIVATION

With a few sera the complement-binding strength or titer was determined in both the active and inactive states. These experiments were performed with the Noguchi technic and the final results are shown in

TABLE 4.—COMPLEMENT-BINDING STRENGTH OF ACTIVE AND INACTIVE SERUM.

Diagnosis.	—Active Serum.— Titer. c.c.	Ratio of Serum to Complement.	—Inactive Serum.— Titer. c.c.	Ratio of Serum to Complement.
SYPHILITIC SERA.				
Syphilis (secondary)	0.008	1:5	0.02	1:2
Syphilis (secondary)	0.01	1:4	0.02	1:2
Syphilis (secondary)	0.008	1:5	0.01	1:4
Syphilis (tertiary).....	0.008	1:5	0.02	1:2
Syphilis (of liver)	0.0006	1:66	0.0008	1:50
Ascitic fluid of above.....	0.008	1:5	0.02	1:2
NON-SYPHILITIC SERA.				
Carcinoma	.... .02	1:2	0.12	1:⅛
Anemia	.... .02	1:2	0.12	1:⅛

Table 4. This series includes the blood from four cases of syphilis with skin manifestations, one of syphilis of the liver and spleen with ascites, and the ascitic fluid from the latter patient. Unfortunately, in only two non-syphilitics who gave the reaction was there sufficient serum obtained to complete this series of tests.

With the syphilitic sera the rate of loss varied, but in general from two to two and one-half times as much inactive as active serum was required, although with two of the sera the loss was not so marked. A similar variability was noted by Boas.[7] With the non-syphilitic sera six times as much inactive as active serum was used.[11] Two examples are

11. Noguchi has found the rate of loss in a case of leprosy to be three. This closely corresponds with the rate he has obtained with syphilitic sera. (Personal communication.)

not enough for definite conclusions, but with the cases shown in Table 3 the rate is usually more than four. This in general would allow the use of 0.08 cubic centimeter of inactive serum as a safe margin for the elimination of non-specific reactions, while, on the other hand, the quantity is tion of non-specific reactions, while, on the other hand, the quantity is sufficient to detect the complement-binding substance in most syphilitic sera.

The results seem to indicate that it is safer to use inactive serum in applying the test for diagnosis. Whether active or inactive serum should be employed in making the test for prognosis and as an indication for treatment is still an open question. There is no doubt that in a large series of tests more strongly positive reactions will be obtained with active serum, but the fact that other diseases give the test much more often than with inactive leads one to doubt whether it is wise ever to use the serum in the fresh state. The total number of reactions is nearly as high with inactive as active serum; the difference is in the intensity of reaction. The percentage of reactions obtained with the inactive serum is as high as the best figures so far published for the Wassermann reaction. It seems to me that if we take any slight inhibition as indication for further treatment, as is done by Lesser,[12] with the Wassermann reaction, the use of inactive serum will give sufficiently delicate results. Still the question is open to discussion and is one that only the results of a long period of experimentation can answer.

CONCLUSIONS

1. Although the use of active serum gives more delicate results in syphilis, it is not to be recommended, because it gives too high a percentage of reactions with non-syphilitic sera.

2. When inactive serum is employed in the proportion of twice the amount of guinea-pig serum a high percentage of positive reactions is obtained in syphilis; and non-syphilitic sera, giving a positive reaction with active serum, give a negative reaction when the same serum is inactivated.

3. The use of inactive serum instead of active renders the Noguchi method more accurate and nearly as convenient as originally described, and still easier of application than the Wassermann method. The amount of blood required can readily be obtained without resorting to venous puncture, so that it is possible to make frequent tests without too much inconvenience to the patient.

The material for this study was obtained through the kindness of Drs. J. A. Fordyce, Joseph Collins, John Van der Poel, A. R. Stevens, H. F. Nordeman and members of the house staff of Bellevue Hospital. I wish to take this opportunity of expressing to them my thanks.

80 West Fortieth Street.

12. Lesser, F.: Deutsch. med. Wchnschr., 1909, xxxv, 379.

ULCERATION OF THE STOMACH AND NECROSIS OF SALIVARY GLANDS RESULTING FROM EXPERIMENTAL INJECTION OF BILE SALTS*

ANDREW WATSON SELLARDS, M.D.
BALTIMORE

INTRODUCTION

In the bodily economy, the bile salts are carefully retained by the organism, being reabsorbed from the intestines, and their physiologic functions may at least be regarded as essential to a normal degree of health. In contrast to their beneficial action, investigations have shown that the bile salts are a very general tissue poison.[1, 2] It is instructive to note the various pathologic lesions to which they might give rise and the corresponding methods of defense which the body possesses.

One of these methods consists in a specific action of the blood serum by which it effectively inhibits the toxic properties of the bile salts.[2] A striking example is the protection of the red corpuscles from hemolysis. There are also certain mechanical considerations which are of importance. Ordinarily the direction of flow and the anatomic continuity of the bile passages is sufficient to protect the stomach, pancreas and peritoneum from contact with bile. Under exceptional circumstances bile may be ejected directly into the pancreas and the resulting conditions have been repeatedly emphasized. Other than hemorrhagic pancreatitis, there appear to be no lesions ascribed to the bile and it is noteworthy that various tissues of the body are so efficiently protected. When bile salts are introduced into the peritoneal cavity, a very definite lesion, however, is produced in the stomach.

EXPERIMENTAL PART

The materials used for the production of the gastric lesions were as follows: The animals chosen were rabbits and guinea-pigs. Both bile itself and bile salts were tested, using beef-bile and sodium glycocholate. The bile salt was dissolved in 5 per cent. concentration in physiologic sodium chlorid solution and, in either case, the beef-bile or the bile salt solution was sterilized by steam at 15 pounds' pressure.

---

* From the Biological Laboratory of the Medical Clinic and from the Pathological Division of the Hunterian Laboratory, Johns Hopkins University.

1. Rywosch: Ueber die giftige Wirkung der Gallensäuren, nebst einen Anhänge über die Giftigkeit der Gallenfarbstoffe (Bilirubin und Biliverdin). Inaug. Diss., Dorpat, 1891.

2. Bayer: Biochem. Ztschr., Berlin, 1908, xiii, 215.

DESCRIPTION OF STOMACH LESIONS

The stomach lesions result very constantly when guinea-pigs are injected with the minimal lethal dose of sodium glycocholate. The following data were obtained from a series of seven animals, all of which gave similar results. For animals of 250 to 270 grams weight, 0.1 gram of sodium glycocholate was injected intraperitoneally. The first definite symptom following the injection was the onset of hiccoughing, which usually began after one to two hours. The rate was irregular at first, but gradually became more frequent and more regular, being sometimes as high as 60 per minute. It is interesting to note the constancy of this symptom in connection with the lesions which developed in the stomach. During the first two or three hours the respiratory rate was often too rapid to be counted. The animals gradually became comatose, the hiccoughing became less frequent and less regular and death resulted within eight to fifteen hours.

Autopsies immediately after death showed well-marked edema of the abdominal walls, free fluid often dropping from the incision. The peritoneal cavity usually contained a slight exudate rich in red and white corpuscles without hemolysis. This would indicate that there was no free bile salt in the peritoneal cavity. Exceptionally, small foci of hemorrhage occurred in the lungs and also in the intestines. In a single instance the tip of a seminal vesicle was filled with blood. No macroscopic changes were observed in any other organs except the stomach. Here there were large areas of hemorrhage with free blood in the gastric contents. The accompanying plate shows a characteristic result. The lesions are sharply localized and, in the main, they avoid the larger blood vessels, producing marked ulceration of the wall itself, while only the serous surface remains intact and the other coats are replaced by blood clots. Wide variation occurs, in different individuals, in the size and number of the lesions. They are always multiple, but sometimes one lesion, as large as one-quarter of the entire stomach, may occur in the fundus. When excessive doses of bile salt were injected so that death occurred in one to two hours, no localized lesions were obtained, but the entire mucosa was infiltrated with blood.

Histological examination confirmed the gross appearance. The smaller ulcers were slightly crater-shaped, the most extensive destruction taking place in the mucosa with less and less erosion of the succeeding layers. Either the muscular or serous coat formed the base of the ulcers. Some areas showed marked diapedesis. There were no signs of thrombosis. The sections afforded little evidence as to the mechanism by which the ulcers were produced.

METHOD OF INJECTION AND EFFECT OF DOSAGE

Further observations were made to determine the effect of various methods of injection and the minimal dosage necessary to produce lesions. The results showed that either the intraperitoneal or the subcutaneous methods could be used. Doses as small as 0.03 gram of sodium glycocholate, when repeated every day, gave definite typical lesions after two or three injections. The intravenous inoculation of lethal doses into the ear vein of rabbits gave rapidly developing respiratory complications followed by death in a few minutes. Small repeated injections, intravenously, were not tried extensively on account of the necrosis and sloughing along the veins, following even the injection of beef-bile. The following is a brief summary of the protocols:

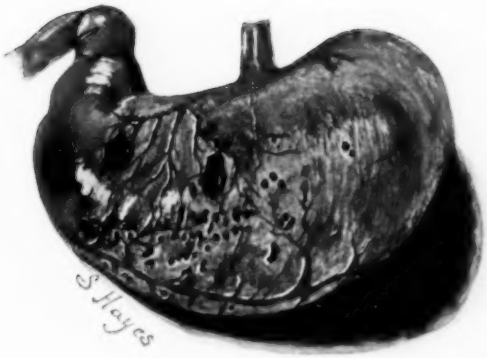
A guinea-pig (300 grams) was injected intraperitoneally with 0.025 grams of sodium glycocholate, or about one-quarter of the lethal dose. No symptoms developed and, after twenty-four hours, anatomical examination showed one small area of ulceration with hemorrhage, situated anteriorly on the lesser curvature. With the expectation of obtaining better defined lesions, small repeated doses were tried.

A second pig (320 grams) received two doses intraperitoneally of 0.03 gram each, twenty-four hours apart. Death occurred on the third day. The autopsy showed four characteristic lesions, three of which were situated toward the pyloric extremity and one in the fundus. There was also an accompanying peritonitis.

A duplicate of this experiment gave no lesions in the stomach but ulceration with perforation of the duodenum occurred about 3 cm. from the pylorus. This was also accompanied by peritonitis.

Small repeated doses were then injected subcutaneously. A pig (280 grams) received 0.03 gram doses for three successive days, death occurring nine hours after the last injection. The injections were made over the hips. The skin was almost completely dissected away from the underlying tissue over the entire thorax, back and abdomen. There was a considerable amount of free fluid which was sterile and almost clear. From one axillary fossa alone 2 c.c. of fluid were collected. The stomach showed five small but distinct lesions on the lesser curvature, three of which were situated anteriorly and two posteriorly. A single lethal subcutaneous injection (0.12 gram for a 310-gram pig) gave seven definite lesions, of variable size and distributed rather generally over the stomach.

Corresponding results were obtained by the injection of beef-bile into rabbits. For rabbits weighing 1000 grams a dose of 15 c.c. was usually fatal in a few hours. A rabbit weighing 1500 grams was injected intraperitoneally with 4 c.c. of bile. The same injection was repeated on the second day, and on the sixth day 7 c.c. were given. A slight loss of weight (150 grams) was the only change noticed. The animal soon regained this weight and a month after the last injection was in good condition. Anatomical examination at this time showed numerous focal lesions throughout the stomach consisting of defects in the mucosa and evidences of old hemorrhage. Two repetitions of this experiment were carried out, with the exception that the animals were sacrificed on the seventh day. In one animal the stomach was practically normal. In the other, in addition to the ulcerations and hemorrhages, there were large edematous blebs under the serous coat around the lesions. The intraperitoneal injection in a rabbit of 0.2 gram sodium glycocholate resulted in lesions similar to those produced in the guinea-pigs.



Anterior wall of stomach showing ulcerations and hemorrhages from bile salts.

RELATION TO GASTRIC ULCER

The lesions which have been described are of especial interest in connection with gastric ulcer as it occurs in human pathology. In the attempts to reproduce gastric ulcer, agents in great variety have been used, including both natural and artificial means, such as disturbances of the innervation and circulation, mechanical injury, the use of various chemicals, of bacteria, and of bacterial products.[3] From this variety of methods, which have been more or less efficient, it would appear that the stomach is especially susceptible to ulceration. The introduction of sodium glycocholate into guinea-pigs does not, however, represent foreign material, but is practically equivalent to the reinjection of bile of the same individual. The position of the lesions, when acutely produced by a single large dose, bears no relation whatever to the customary position of gastric ulcers. In the more chronic cases, however, where small daily injections were made, the lesions were always small, fewer in number, and showed something of a tendency to appear toward the pyloric extremity around the lesser curvature. In the cases of gastric ulcer in which surgical methods are used for the relief of hemorrhage, it is often found that the bleeding does not occur from any single point, but that there are many bleeding points over the stomach. Apparently hemorrhage is a more prominent feature of the lesions produced by bile salts than it is in the case of other ulcerative agents which have been reported.

MECHANISM OF THE PRODUCTION OF THE LESIONS

The mechanism of the production of these gastric lesions is not entirely clear. It has been observed clinically that hemorrhages are common in jaundice. This is probably due to the endothelial lysis and to the delayed coagulation time.[4] It has also been found that the autolysis of various tissues is inhibited by blood serum.[5] The stomach, of course, should be especially liable to autolysis on account of its protein ferments. In view of the pronounced inhibiting effect of bile salts and blood serum on each other,[2] it is conceivable that, in the presence of bile salts, the serum no longer protects the stomach against its own ferments and the ulceration of the various coats occurs, accompanied by the ordinary hemorrhage of jaundice.

Other possibilities suggest themselves. At present the phenomena of anaphylaxis have attracted considerable attention. In a preliminary experiment no hypersusceptibility could be developed toward the bile salts.

3. Rosenau and Anderson: Jour. Infect. Dis., 1907, iv, 1.
4. Wells: Chemical Pathology, 1907, p. 408, ed. 1.
5. Longcope: Jour. Med. Research, 1908, xviii, 45.

This result would accord with the finding that, thus far, anaphylaxis has been obtained only with proteins.

Three guinea-pigs were injected intraperitoneally with 0.05, 0.01 and 0.005 gram sodium glycocholate, respectively. After one month the injection was repeated, using 0.05 gram for each animal. No symptoms developed.

In some of the rabbits, the gastric contents were markedly bile-stained and responded to Pettenkoffer's test for bile salts. Subsequent investigation did not give satisfactory evidence of a true secretion into the stomach. Under proper controls, with section of the pylorus and duodenum to prevent regurgitation, after the introduction of sodium glycocholate into the peritoneal cavity, an alcoholic extract of the stomach contents gave Pettenkoffer's reaction. In this instance, the amount of hemorrhage from the stomach lesions was so great that the blood alone which escaped could have contained sufficient bile salt to give the reaction.[6]

SPECIFICITY OF THE LESIONS

The ulceration and hemorrhage which follows the subcutaneous or intraperitoneal injection of bile salts is relatively specific for the stomach, occurring almost constantly in this organ. Much less constantly, relatively small foci of hemorrhage were noted in other organs, especially in the lungs and intestine. Lesions in the pancreas were not obtained.

It has generally been considered that the inflammation following the direct injection of bile into the pancreas is specific and that analogous lesions do not occur in other organs. The explanation has been offered that the protein ferments liberated in the initial injury to the pancreas take a part in the process.[7] This explanation was studied from two standpoints: First, injections of bile salts were made into glands which do not secrete a protein ferment, and, second, the toxicity of the pancreatic ferments was studied by hemolytic methods.

INJECTIONS OF BILE SALTS INTO THE PAROTID GLAND

The salivary glands were chosen as a type of tissue in which there would be no protein ferment to complicate the process. Injections were made into the parotid gland of dogs, using sodium taurocholate, since this is the salt which is most prominent in dog's bile. The parotid duct was exposed by a skin incision

6. In various animals, after death from bile salts, Rywosch (Inaug. Diss., Dorpat, 1891) frequently found that the intestinal contents were bloody and the intestine itself showed marked hyperemia with submucous inflammation. The explanation offered was that a disturbance of the heart's action resulted in passive congestion with endothelial lysis of the blood-vessels due to the action of the bile salts.

7. Opie: Diseases of the Pancreas, 1903, p. 130, ed. 1.

over the masseter muscle. Three cubic centimeters of varying concentrations of sterile bile salt solution, dissolved in physiological saline, were injected from an ordinary syringe. In all cases only one parotid was injected, the other being reserved for a control. After twenty-four hours, both glands were removed. In the first two experiments 2 and 5 per cent. concentrations were tested. No swelling or local change occurred, but, in both instances, the glands, on removal, showed definite lesions. A third dog was injected with a 13 per cent. concentration such as was used by Flexner[8] in working with the pancreas. No macroscopic change took place in the gland, but there was extreme edema, most marked at the site of operation and extending into the surrounding tissues. Apparently the bile salt had escaped from the gland and the experiment was repeated, ligating the duct immediately after injection. The edema of the neighboring parts did not occur and lesions took place in the gland, a little more severe perhaps than those where weaker solutions were used.

On removal, the injected parotids, as compared with those of the control side, were almost twice as large, somewhat firmer, and were distinctly red in color as contrasted with the normal grayish color. Free blood clots were not obtained, such as Opie usually found in corresponding experiments on the pancreas. In the second experiment, using a 5 per cent. bile salt solution, in addition to the injection into the parotid, an exactly duplicate injection was made into the submaxillary duct. On removal, the submaxillary gland was enlarged, very firm, bright red in color, and the interlobular spaces were everywhere filled with blood clots. In this experiment the possibility of mechanical injury to the gland itself could not be excluded, but the very general distribution of the lesion would speak against such an error.

The microscopical examination of the injected salivary glands reveals a very intense alteration in the tissue, evidently produced by the injected material. The secreting tissue is completely necrotic wherever the bile salt reached the lobule of the gland. In many cases the adjacent connective tissue is also completely necrotic for a considerable distance, and in the margin of such an area there is an intense inflammatory reaction. There are, however, no extensive hemorrhages such as are found in acute hemorrhagic pancreatitis.

The lesions in the parotid apparently correspond most closely to those cases in the pancreas in which only a diffuse diapedesis resulted, without free extravasation of blood.[9] The differences in the lesions of the two glands might be considered as differences of degree rather than as two separate types of lesion.

HEMOLYTIC ACTION OF THE PANCREATIC FERMENTS

Recent investigations have emphasized the toxicity of the pancreatic ferments, rapidly fatal results being obtained in animal experimentation.[10] Results of interest were obtained for the hemolytic action of the

8. Flexner: Jour. Exper. Med., 1906, viii, 167.
9. Opie: Johns Hopkins Hosp. Bull., 1901, xii, 182.
10. Guleke: Arch. f. klin. Chir., 1905-6, lxxviii, 845. Doberauer: Beitr. z. klin. Chir., 1906, xlviii, 456.

ferments of the pancreas and other tissues. Similar studies have also been made by Korschun and Morgenroth[11] in investigating the source of serum hemolysins.

The following technic was employed. All dilutions and extractions were made with physiological salt solution. Pancreatic ferments were obtained by grinding the whole pancreas with sand and adding three times its weight of salt solution. The mixture was strained through a towel and a 1 to 10 dilution of this extract was used as a stock solution. No activation was necessary other than that obtained from the injury to the cells in grinding. As a control, other glands were extracted in the same manner. The hemolytic mixtures consisted of 1 c.c. of various dilutions of the glandular extracts and 0.5 c.c. of a 5 per cent. emulsion of corpuscles which had been washed three times. This gave a final volume of 1.5 c.c. in each case. Dogs were used for the experiment and the extracts were always tested against corpuscles of the same individual. The animals were always bled to death, but no special measures were taken to remove the remaining blood from the organs. The preparations were incubated at 37 C. for two hours and then allowed to sediment over night at 8 C.

In a preliminary experiment complete hemolysis was obtained by a pancreatic extract in a dilution of the fresh gland substance corresponding to 1 part in 9,000, while for an extract of the stomach a 1 to 400 dilution, and for the thyroid a 1 to 90 dilution was required. A single test of extracts of the parotid and submaxillary glands and of the liver gave no hemolysis in 1 to 50 concentrations. The spleens of three animals were tested. Two gave no hemolysis at all, but one gave complete hemolysis up to a 1 to 900 dilution.

Further experiments were then made with the pancreas from another individual. The same activity was found as for the first gland tested. Its action was effectively inhibited by a relatively small amount of serum. The inhibitory effect of the serum was not appreciably affected by a temperature of 95 C.

The accompanying table gives the experimental data. Dog serum was obtained from the same individual from which the pancreas and corpuscles were taken. A 1 to 10 dilution was made up and the amount of corpuscles required for a 5 per cent. emulsion was added directly to the diluted serum, in order not to increase the total volume of 1.5 c.c. for the final mixtures. The dilutions are given in terms of the fresh gland tissue. The final dilution of the serum after the addition of the pancreatic extract is 1 to 30.

TABLE SHOWING HEMOLYSIS BY PANCREATIC EXTRACT AND ITS INHIBITION BY NORMAL SERUM

Pancreas Extract, 1 to —	Salt Solution.	Normal Serum, 1 to 30.	Serum 1-30, Heated 20 min. at 95° C.
500	Complete	Complete	Complete
900	Complete	None	Partial
1,800	Complete	None	None
5,000	Complete	None	None
9,000	Complete	None	None
15,000	None	xx	xx

These results are exactly analogous to those which have been obtained in corresponding experiments with bile salts.[12] Judging from the hemolytic experiments, the hemorrhage occurring in pancreatitis would tend

11. Korschun and Morgenroth: Berl. klin. Wchnschr., 1902, No. 37, xxxix, 870.
12. Johns Hopkins Hosp. Bull., 1908, xix, 268.

to neutralize the action of the pancreatic toxins as well as the bile salts. There is no theoretical reason why the protein ferments of a gland should not augment a lesion initiated by the bile, or even why the injection of pancreatic ferments, for example, should not excite a lesion.

In catarrhal jaundice, unless the pancreatic duct escapes from the inflammation, it is possible that the pancreatic toxins, as well as the bile, might gain access to the circulation.

CONCLUSIONS

1. The injection of guinea-pigs with the lethal dose of sodium glycocholate produces lesions in the stomach which are relatively specific. These lesions are closely analogous to those produced by the direct injection of bile into the pancreatic duct.

2. Injection of sodium taurocholate into the parotid gland of dogs produces lesions which are less extensive than for corresponding conditions in the pancreas.

3. An extract of the pancreas is actively hemolytic *in vitro*. Its behavior toward blood serum and corpuscles in test-tube experiments is exactly analogous to that of the bile salts. The pancreatic ferments might, theoretically, augment the lesions produced, *in vivo*, by bile. The hemorrhage in the acute pancreatitis caused by bile would, judging from the hemolytic reactions, tend to neutralize both the toxic action of the bile salt and also of the pancreatic secretions.

I take this occasion to recognize the very material assistance of Dr. R. I. Cole and of Dr. W. G. MacCallum during this investigation.

Manila Bureau of Science, Manila, P. I.

THE EFFECT OF HEXAMETHYLENAMIN ON GUINEA-PIGS*

CHANNING FROTHINGHAM, JR., M.D.
BOSTON, MASS.

Hexamethylenamin, or, as it is commonly called, urotropin, was first prepared in 1860 by Butlerow.[1] It is made by the action of ammonia on formaldehyd. It is readily broken up by heat, some acids, etc., into formaldehyd and ammonia. Nicolaier[2] first introduced this drug into medicine in 1894. He concluded that it stimulated the secretion of urine, prevented the growth of bacteria in the urine, and acted as a solvent of uric acid calculi. In some cases he gave as much as 150 grains in a day without producing symptoms. On the other hand, smaller doses after prolonged use would occasionally cause burning in the region of the bladder, and the appearance of epithelial cells in the urine. If the drug was still continued red blood corpuscles would appear in the urine. As a result of these observations many men began to employ this drug. Casper[3] and Mendelsohn[4] showed that it did not act as a solvent of uric acid calculi within the body. They and other authors, especially Richardson,[5] confirmed Nicolaier's views in regard to the power of hexamethylenamin to act as a urinary disinfectant, especially in typhoid fever. Casper also thought that it was of value in curing phosphaturia. From that time on urotropin has been used in typhoid fever and in cases of cystitis and pyelitis due to other agents than the gonococcus or tubercle bacillus.

The fate of hexamethylenamin within the body has not been definitely decided. It has been reported as present in the blood and urine. Casper[3] has found free hexamethylenamin in the blood of a rabbit after a subcutaneous injection of the drug.

Richardson[5] found that in cases with an existing nephritis the administration of hexamethylenamin not only did not cause an increase in albu-

---

* From the Laboratory of the Department of Theory and Practice of Physic, Harvard University. Published with the approval of the Committee on Fellowships as a part of the work done under a grant of a Bullard Fellowship, 1908-1909.

1. Butlerow: Ann. d. Chem. u. Pharm. (Liebig's), 1860, 115-332.
2. Nicolaier: Deutsch. med. Wchnschr., 1895, 541.
3. Casper: Deutsch. med. Wchnschr., 1897, Therap. Beilage, p. 75.
4. Mendelsohn: Berl. klin. Wchnschr., 1898, 48.
5. Richardson: Jour. Exper. Med., 1899, iv, 19.

min and casts, but in some cases apparently caused a diminution of these elements.

Since the introduction of hexamethylenamin in therapeutics reports have been gradually accumulating of evil effects caused by this drug. In the cases reported the amount of the dose and the length of time over which the drug were given vary greatly. Even in the same individual the same dose acts differently at different times. Coleman,[6] from the literature and his own experience, reported in 1903 the following list of symptoms in human cases following the use of hexamethylenamin, which in some of the cases had been given in small doses: Irritation of the stomach, diarrhea and abdominal pain, irritation of the skin with a rash like that of measles, headache and ringing in the ears, irritation of the kidney and bladder, hematuria, and hemoglobinuria. In these cases Coleman thinks that the blood is probably derived from the bladder. In 1906 Karwowski[7] and Rosen also summed up the ill effects which might arise from hexamethylenamin, but did not add anything essential to the report of Coleman.

As a result of all these communications hexamethylenamin, in small doses, is considered a safe drug for most people, and also in large doses up to the appearance of symptoms. When symptoms appear the discontinuance of the drug causes a subsidence of the symptoms. None of these writers, however, have inquired into the tissue changes back of these symptoms.

In 1908 Crowe[8] showed that typhoid bacilli could be killed in the gall bladder of man as well as in the urine by the administration of hexamethylenamin provided that sufficiently large doses were used. He demonstrated the presence of hexamethylenamin in the bile, cerebrospinal fluid, synovial fluid, saliva, pleural effusions and blood of man. Also he asserted that it acted favorably on other forms of infection in cavities where the hexamethylenamin was found present. For killing typhoid bacilli in the gall bladder 75 grains a day for several days are necessary. As a result of these findings it seems possible that even larger doses might be of value in other infections.

In view of the fact that as a result of Crowe's work hexamethylenamin might be used in large doses the following experimental work was done to see if possibly any lesions could be found in any organs after the administration of large doses. As such work could not be tried out in human cases guinea-pigs were used.

6. Coleman: Medical News, New York, 1903, lxxxiii, 393.
7. Karwowski: Monatschr. f. prakt. Dermat., 1906, xlii, 8.
8. Crowe: Johns Hopkins Hosp. Bull., 1908, xix, 109.

There were three main problems to be solved in doing this work: 1. How much hexamethylenamin per body weight can be given to a guinea-pig without producing fatal symptoms? 2. What lesions, if any, are produced by one or two very large or fatal doses of this drug? 3. What lesions, if any, appear after repeated sublethal doses?

In these experiments the hexamethylenamin was dissolved in sterile water and injected subcutaneously.

Guinea-pigs vary somewhat in their ability to withstand the drug, but as a rule 4½ to 5 grains per ounce of body weight will kill the pig or render it very quiet for twelve to fourteen hours. One pig, however, survived a dose of 6½ grains to the ounce. As it takes a considerable amount of boiled water to put a fatal dose of hexamethylenamin into solution, one pig, as a control, was injected with this amount of water. The animal did not suffer any ill effects. If the dose proves fatal it usually does so within a few hours. If the animal survives twenty-four hours it recovers. After a fatal dose the pigs grow more and more quiet, and in the course of two or more hours usually topple over, have some slight twitching of the extremities, and gradually die. Others have been found in a sitting position, which suggested that they grew more and more quiet and then died. In none were any convulsions noted.

The pigs are able to withstand sublethal doses over a considerable period of time without any ill effects other than reaction at the point of injection and some quietness for a few hours after the injection. By the next day, however, they are lively again. One animal weighing 20 ounces, for instance, received 375 grains in eight doses during nine days. The doses were each 45 grains, except one of 60. Five days after the last injection the animal appeared lively and perfectly well, showed some reaction at the site of inoculation, which was rapidly improving and had lost only 2 ounces in weight. On that day it received a fatal dose. Another pig, weighing 18 ounces, took 15 doses in nineteen days, amounting in all to 319 grains, and gained 1 ounce in weight. Eight or nine days later it was given 75 grains, which it survived, and two weeks later had gained 2 ounces.

In the animals which received one or two large doses the findings were practically the same, whether the doses proved fatal or not. At the point of inoculation there was edema of the subcutaneous tissue and muscle, with congestion and some hemorrhage. Of the twelve guinea-pigs in this group, two showed free fluid in the peritoneal cavity. Both of these received fatal doses. It was felt at the time that one of these animals received some of the injection intraperitoneally; and this suspicion was practically confirmed at autopsy by a subperitoneal hemor-

rhage on the stomach wall near the site of suspected entrance of needle. As none of the other ten pigs in this group showed free fluid, it seems fair to assume that the other case of free fluid was due to a perforation into the peritoneum while injecting the animal.

In these twelve animals there were no macroscopic lesions of any organs other than those mentioned above, except in the stomach. In eleven of these twelve cases the stomach was examined and in two cases submucous hemorrhages were present. These areas will be referred to later under the microscopic findings.

Pieces of tissue from the heart, lungs, liver, spleen, kidneys, stomach, adrenals, bone marrow, brain, muscles and abdominal wall were preserved in Zenker's fluid and formalin. Sections mounted in paraffin and stained with eosin and methylene blue from two of these cases, one with one dose and one with two doses which proved fatal, were studied. Also three control guinea-pigs which had not received hexamethylenamin were studied. The hearts in these two cases showed an occasional area of round-cell infiltration, but otherwise were negative. The controls showed the same. The lungs showed an increase of leucocytes and lymphocytes around the vessels and bronchi, and occasionally a slight cellular infiltration into some of the alveoli. The controls showed the same. In the liver there was considerable vacuolization of the cells in both the injected animals and the controls. In one of the injected animals there were areas of necrosis of the parenchymal cells with invasion by phagocytic cells. They did not appear in any of the other injected animals of this or the other group and was attributed to chance focal necrosis in the liver, which is apt to occur in guinea-pigs, as Mallory[9] has pointed out. The spleens are congested and show questionable hemorrhages around the edges of the lymph follicles, but the controls show the same. Pigment in the endothelial phagocytic cells in some cases was marked in both the injected animals and in the controls. In the kidneys of these two pigs were a few scattered areas of round-cell infiltration apparently replacing some of the kidney parenchyma. The controls presented the same appearance. In none was there any evidence of extensive destruction of the tubules or injury to the glomeruli. In one of the cases many of the nuclei of the convoluted tubules stained a solid purple and had lost their vesicular appearance. Under high power faint, round, pinkish bodies could be made out in the purple mass. As no other cases showed this condition it was considered as a freak of fixation, or an accidental lesion, rather than a lesion attributable to the hexamethylenamin. The adrenals,

9. Mallory: Jour. Med. Research, 1901, vi, 264.

muscle, bone marrow, duodenum, cerebrum and cerebellum were practically the same in appearance as the controls and all apparently normal. The abdominal wall at the site of inoculation showed edema of the tissues and necrosis of some of the muscle fibers, with invasion of phagocytic endothelial cells and polynuclear leucocytes. In addition, the surrounding edematous tissues often contained large numbers of polynuclear leucocytes.

The stomach was examined microscopically in eight of these cases, including the two which showed submucous hemorrhages in the gross. The six which showed no lesion in the gross did not show any lesion other than a congestion of the vessels throughout all the layers. Both of the stomachs which showed submucous hemorrhages presented microscopic lesions. In one there was marked congestion of all the vessels and hemorrhage into the mucosa. Also the mucosa was necrotic in places; and surrounding these necrotic areas were leucocytes wandering toward the necrosed area. This reaction on the part of the leucocytes was present throughout all layers of the stomach wall in the vicinity of the necrotic areas. In the other case the congestion and hemorrhage were not so marked, but the necrotic mucosa had been eroded in one place down to the submucosa. This was the only necrotic area in the sections from this animal. Surrounding this area, as in the other case, there was evidence of activity on the part of the leucocytes. The stomachs from seven pigs, as a control, were examined, and they showed nothing abnormal in the gross or under the microscope. The vessels in the controls were not so much congested as those in the animals injected.

Rosenau and Anderson[10] in 1906 showed that hydrocyanic acid and chloral-cyanhydrin caused hemorrhagic areas in the stomach wall of guinea-pigs when given in fatal doses. They did not give in their paper the microscopic description of these areas. It seems probable, however, that some evidence of necrosis would have been present in these areas. This congestion and hemorrhage with necrosis that may occur after hexamethylenamin must be looked on as a lesion which may occur in guinea-pigs after lethal or very large doses of several drugs, and not as specific to hexamethylenamin.

Five guinea-pigs received sublethal doses for a period of a week or more. The one observed the longest was watched forty-four days, on sixteen of which he received doses of hexamethylenamin varying from 7½ to 75 grains. Of these five animals three were chloroformed apparently in good health and two received fatal doses after many sublethal pre-

10. Rosenau and Anderson: Bull. 32, Hyg. Lab. U. S. P. H. and M.-H. S., 1906.

ceding ones. The animals showed the same subcutaneous lesions at the point of inoculation as described above. One animal had free fluid in the abdominal cavity. This animal received a fatal dose at the end of eight days, but here again it was suspected that some of the drug was given intraperitoneally. One of these animals that received a fatal dose after six former injections showed a small submucous hemorrhage of the stomach. Only one other stomach was examined in this group, but it did not show anything abnormal. All five of these cases were examined microscopically, and they showed nothing different from the other case described under the other group and the controls. The stomach in the animal that had the hemorrhage in its stomach wall simply appeared congested. Presumably the hemorrhagic area was missed in the sections examined.

In conclusion it may be said that hexamethylenamin, when given subcutaneously in guinea-pigs, either in single doses or in repeated doses, produces necrosis of the muscle and cellular reaction at the point of inoculation. It also causes congestion of the stomach vessels, and in some cases hemorrhage into the mucosa, with ulcer formation.

This work offers no proof as to what lesions in man may be the cause of the symptoms occasionally produced by hexamethylenamin, but it suggests that these lesions are not organic. The most interesting points brought out are the enormous amount of hexamethylenamin a guinea-pig can receive subcutaneously without apparent injury and the fact that hexamethylenamin is another drug to add to the list of those that may cause hemorrhage in the stomach walls of guinea-pigs.

51 Hereford Street.

RESULTS OF TUBERCULIN TESTS IN MONKEYS AT THE PHILADELPHIA ZOOLOGICAL GARDENS*

C. Y. WHITE, M.D., AND HERBERT FOX, M.D.
PHILADELPHIA

INTRODUCTION

We have not thought it necessary to review the general literature on the subject of injections of tuberculin for diagnostic purposes. Much has been written on this subject in regard to both human beings and domestic animals. We have, however, been able to find comparatively little on the use of this valuable test applied to wild animals. The opportunity has presented itself to us to follow out the test in the monkeys of the Zoological Gardens of Philadelphia while we were serving in the capacity of pathologists. We present in the following paper the result of our observations on tuberculin as a diagnostic agent in these animals.

The use of this test was started in 1905, and has been continued to the present. It has been noted in Philadelphia that the average life of a common monkey on exhibition varied between eighteen and twenty-one months. It has been found on examination that the great majority of these animals died of tuberculosis. What is true in Philadelphia is probably true in zoological gardens in other parts of the world. This high mortality from tuberculosis led us to adopt some measures to prevent the admission of infected animals and to isolate those already diseased. To accomplish this end the value of the tuberculin test was tried. We began this testing on the stock of monkeys then on exhibition, but very soon found that these were in the advanced stage of tuberculosis and our results were far from satisfactory. It was decided by the officers of the Zoological Society that the infected stock should be destroyed, the monkey house thoroughly cleaned and disinfected, and that thenceforth only those monkeys should be placed on exhibition which failed to react to injections of tuberculin. All incoming monkeys were therefore placed in quarantine in the laboratory and carefully studied as to their general condition. Our observations were directed toward the state of gastrointestinal tract, nervousness, thirst, coughing, and the temperature.

---

*From the Laboratory of Comparative Pathology of the Zoological Society of Philadelphia.

We encountered, as might have been expected, many difficulties in the early part of this work, chief of these being the determination of the normal temperature of the monkeys. A thorough study of the normal temperature was our first task, because at that time we had no experience or literary reference to guide us.

The obtaining of the normal daily temperature of the monkeys at a definite time each day was a step in the right direction, but, as will be seen later on, we soon found that even with this daily temperature very much more was to be sought. We found that the temperature of the monkeys varied with the time of day, and to a certain extent with the different species; and, furthermore, that external conditions, such as room temperature, excitation, etc., had an appreciable effect on the record. A further study of this variation showed that the monkeys' temperature fell during the night, while the highest daily temperature was in the neighborhood of 2 to 3 p. m. In other words, the normal monkey's temperature reached the highest point between 2 and 3 p. m., with a gradual fall to its lowest level, which was about 2 or 3 a. m., after which it again rose to the afternoon height.

It was also ascertained that the normal high temperature of a healthy monkey was higher by three or four degrees than that of a normal human being. This average of temperature varied with the species of monkey under observation, but was usually in the neighborhood of 101 and 102 F. at the highest point; the lowest point in these cases was about three degrees lower, and produced, as will be seen in the charts, definite curves, the lower levels of which we have designated as the "night drop." In order to obtain the daily curve of temperature it was found necessary to make records every four hours. By doing this the normal temperature of a healthy monkey showed an uniform curve which reached its highest point at about 3 p. m. and the lowest level at about 3 a. m. Extensive chartings of individual monkeys and the comparison of the temperature of several monkeys showed the uniform curves. The temperature was taken at 7, 11 and 3 because the high and low points were at 3 p. m. and 3 a. m. respectively. It was later found that monkeys of a nervous temperament, those easily excited and those which failed to become accustomed to the taking of temperature, showed variations in the daily curves which could be explained only by the nervous state of these animals.

DETAILS OF THE PRESENT SYSTEM

The monkeys are now received in the quarantine room of the laboratory building. The attendant who has charge of them has had many

years' experience with monkeys and is familiar with their habits. He takes a very lively interest in helping to take the temperatures and in the application of the test. The animals are allowed to remain quiet in cages for some days before observations are started. Preparatory to the injection of tuberculin daily temperatures are taken at 3 p. m., the hour at which the highest temperature point is reached. These daily records are continued until the temperature is seen to maintain an almost even course for about ten days. We have arbitrarily adopted 1° F. as the limit of variation during the observations previous to the injections. If this variation be in the form of a saw-tooth curve the monkey is allowed to rest for an indefinite time until the temperature becomes regular.

The initial record is usually high, owing, no doubt, to the handling incident to the initiation of the test. After the first few doses the records are lower and usually follow a steadier course. The monkeys are usually removed from their cages with covered hands if they be small and tame, while the larger ones are caught in a net. The great majority of the monkeys readily become accustomed to this daily routine, so that by the time they are ready for the actual test little or no excitement is present. The records are made from rectal temperature in all our work. No time is lost after taking the animal from its cage in obtaining the record, so that the excitement may have as little effect as possible. The thermometer, well greased with petrolatum, is inserted three inches along the anterior wall of the rectum and exposed for three minutes. If the temperature record vary several points from the previous daily record, or if there be any doubt of its correctness, it is retaken.

The normal height for a monkey's temperature can not be stated with exactness compared with that of the human being. The temperature of those normal monkeys which have been killed without evidence of tuberculosis will not allow a definite statement as to the normal temperature of monkeys, as a whole, or of the different species. The daily temperature per rectum at 3 p. m. is generally between 101 and 102 F. Some monkeys have passed the test and still live which had an even temperature as high as 104 F. The height *per se* does not seem indicative of the condition of the monkey unless it be quite high or low, such as 105 + or 99 F. These extremes are, however, usually combined with irregularity before and after the injection. Starting at the high point, 3 p. m., the temperature begins with 101 to 102 F. and gradually declines, at 7 p. m. registering 0.4 to 1 F. lower. At 11 p. m. a similar further fall is seen. The low point is reached about 3 a. m., after which a gradual rise occurs following in reverse order the same general

course as the fall during the preceding twelve hours, again reaching the high point at three in the afternoon. The average of this fall in the monkeys tested at this laboratory is 3.5 F. In a healthy monkey it may be as low as 1.8 F., or as great as 7 F. (See Chart 1, black ape No. 9, I 6, which shows a healthy normal four-hour temperature.) The temperature of monkeys is elevated by excitement. This is well shown by Simpson and Galbraith,[1] who studied the temperature of normal monkeys over long periods and the effects of various forms of excitement. They found that the temperature was increased in direct proportion to the degree of excitement. This must be taken into consideration when observing monkeys which do not become accustomed to the excitement incident to taking the temperature. In such cases the temperature must be taken over long periods in order to obtain a definite course of the curves. Occasionally the course of the curves is so irregular that definite conclusions cannot be drawn. Such monkeys are condemned.

TUBERCULIN TEST

Preparatory to the test the monkey is observed as above described. It has been the practice to make the injection in the forenoon to see what rise may follow at the high point on the same day. Small monkeys such as the average common macaque, will receive 1 to 2 mg. Small capucins get 0.75 to 1.5 mg.; an anubis baboon, or long-armed baboon, may receive as high as 3 mg. This dose is rarely exceeded. It will be seen that the dosage is higher than that usually given to human beings, but considerably lower than that given to cattle. This dose was purposely made large because in our early work we found that such doses readily caused tuberculous animals to die, while it had no effect on healthy animals. The injection is given under the loose skin of the flank. We have never seen any local reaction at the site of inoculation. The temperature is then taken every four hours (3, 7, 11, 3, 7, 11) for forty-eight hours. In the case of a normal monkey the course of the temperature curve follows exactly that described above and illustrated by Chart 1. In some normal monkeys a slight variation may be noted in the length of the night drop immediately following the tuberculin injection. It is frequently, but not always, 0.4 to 0.6 F. lower during the first than during the second night. This is, however, not constant or marked enough to allow any diagnostic value to be put upon it. In the case of tuberculous animals the most common occurrence is a rise of temperature within twelve hours after injection. The daily curve may

1. Simpson and Galbraith: Tr. Roy. Soc. Edinburgh, 1906, xiv, Part I. p. 75.

be entirely destroyed, the temperature following instead a course higher than indicated by the previous daily 3 p. m. record. The destruction of the daily curve, with an elevated temperature, is the most significant indication of a positive test—i. e., tuberculosis. Failure to make the normal night drop in a few cases has taught us to be always doubtful of the condition, for we have found that a subsequent test will usually give a positive reaction. In some few cases and for reasons unknown to us the characteristic rise indicative of a positive reaction, does not take place until some time within the second twenty-four hours. In these latter cases we generally speak of the reaction as a "delayed reaction." This delayed reaction has the usual characteristics of a positive test. Here a case may be cited in point. White-throated Cebus No. 27 (D. 7; See Chart 2) showed the temperature series taken many times from September, 1905, to January, 1906. The course was very irregu-

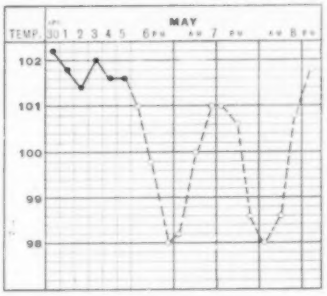


Chart 1 (I 6).—Black ape No. 9; injected May 6, 1907; passed May 10, 1907; died Sept. 27, 1907. Autopsy showed no tuberculosis.

lar at first and he was not injected until Jan. 28, 1906. A rise of 1 F. followed the injection, but the rest of the curve was about normal. He was held over and retested March 23, at which test the curves did not seem low enough. His temperature remained irregular during the summer while he was under observation. In November, 1906, he was tested again after a more regular period. The first day did not fall very low, but followed a regular progression until the 11 o'clock a. m. temperature on the second day, which was the high point instead of 3 p. m. There was a very irregular, shallow curve during the next twenty-four hours and at 3 p. m. on the third day the record was 0.6 F. higher than any previous one in this course. At autopsy the only sign of tuberculosis was in the right bronchial lymph gland, where two small progressive tubercles were found. This well illustrates the desirability of taking

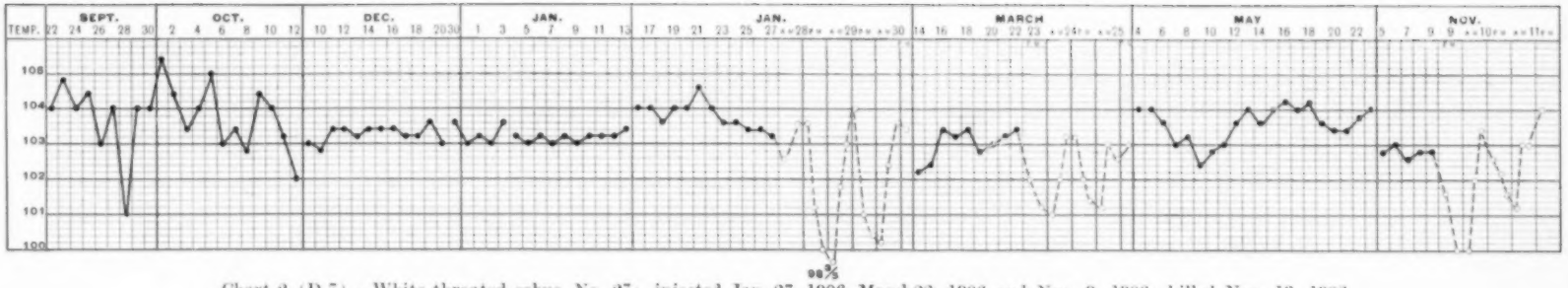


Chart 2 (D 7).—White-throated cebus, No. 27: injected Jan. 27, 1906, March22, 1906 and Nov. 9, 1906; killed Nov. 13, 1906. Autopsy showed two miliary tubercles in right bronchial lymph gland.

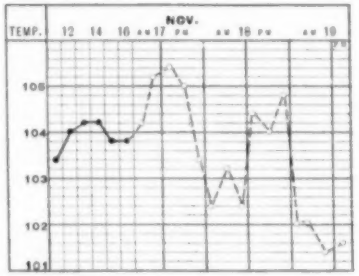


Chart 3 (B 7).—Drill baboon No. 5; injected Nov. 15, 1905; killed Nov. 21, 1905. Autopsy showed pulmonary tuberculosis.

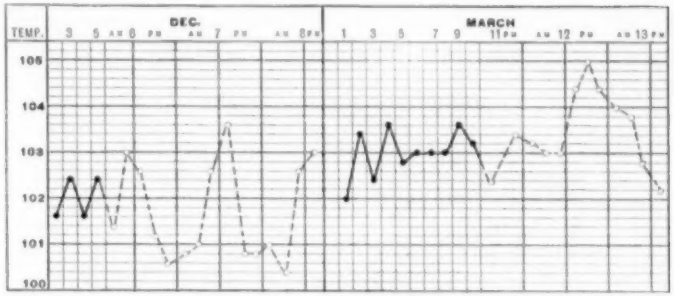


Chart 4 (E 4).—Sooty mangabey No. 62: injected Dec. 5, 1905; passed Dec. 14, 1905; retested in March and found tuberculous.

the temperature two days after the injection, and how minute a lesion will cause a reaction. Good charts of tuberculous monkeys after the test are seen in drill baboon 5 (B 7) and sooty mangabey 62 (E 4), Charts 3 and 4.

The temperature in advanced cases of tuberculosis may fall below the registering point of the thermometer shortly following the test. This is well illustrated by lesser white-nosed monkeys C 2, Chart 5, and pig-tailed macaque No. 69 (A 8), Chart 6. In both of these cases the animal died. We have occasionally noted an unusually deep night drop immediately following the injection in monkeys which were subsequently found on autopsy to be healthy. The temperature of these monkeys showed an approximately normal rhythm, without a rise above the 3 p. m. high point.

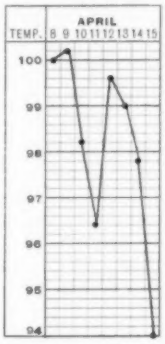


Chart 5.—Lesser white-nosed monkey: died April 16, 1905, after injection of 5 mg. of tuberculin.

The relation of the degree of reaction to the extent or severity of the lesions is a very uncertain one and our experience allows no conclusions on this score with the exception noted above concerning very advanced cases of tuberculosis. The case just cited (D 7, Chart 2) shows a positive reaction and only a minute trace of infection. A black ape gave a most pronounced reaction and had only a few pin-head-sized tubercles in the liver and spleen, while sooty mangabey No. 62 (E 4, Chart 4), drill No. 5 (B 7, Chart 3), gave no more marked reactions and showed advanced lesions at autopsy. Perhaps the rule is for the temperature to fall in the most active and widespread cases.

The number of monkeys received at the gardens and tested during the time these observations have been made is as follows: One hundred and twenty-eight monkeys received; passed, 81; condemned or died at

or near the time of the first injection and not on exhibition, 47. It will be seen from this that only 63.3 per cent. of the monkeys received actually passed the tuberculin test. Of the 81 monkeys which were passed 79 were sent to the monkey house; 5 died there as the result of tuberculosis. They lived one, three, eight and sixteen months. Five others were returned, retested or killed and found tuberculous. The rest remain apparently normal to date. No monkey passed since February, 1906, has as yet developed any sign of tuberculosis. In reviewing the charts of the monkeys dead of tuberculosis and of those associated with them in the cages it is possible to suspect the source of infection of at least several of these animals. The total deaths from tuberculosis among monkeys which had been in the monkey house since the test was begun is ten, of which eight may with reasonable certainty be traced to two infections from cases which occurred early in the tests, of which the temperature charts would not have been passed had we had the experi-

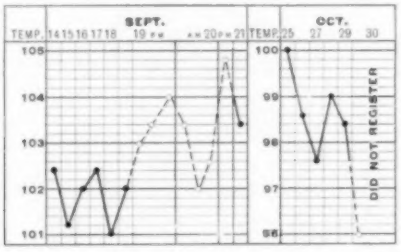


Chart 6 (A 8).—Pigtailed macaque No. 69; injected Sept. 19, 1905, and Oct. 29, 1905; died Nov. 1, 1905. Autopsy showed general tuberculosis.

ence later gained. From March 1, 1907, to March 1, 1908, there were two deaths, and the last death from tuberculosis was on Oct. 17, 1907.

The monkeys which passed the test and showed tuberculosis after being returned from the monkey house for any reason are as follows:

Sooty mangabey, No. 62, passed on forty-eight-hour temperature; returned and found tuberculous after being on exhibition three months.

Sooty mangabey, No. 63, passed on forty-eight-hour temperature; on exhibition three months; injected, gave a questionable reaction; gave a positive reaction eight months after return. The reaction on which it was passed was questionable.

Sooty mangabey, No. 60, passed on forty-eight-hour temperature which was questionable; returned in three months; eight months after return positive reaction, tuberculosis.

Grivet, No. 9, passed on questionable forty-eight-hour temperature; returned in three months; positive reaction; killed, tuberculosis.

Black ape, No. 7 (I 2), passed on twenty-four-hour temperature; returned in three months; gave questionable reaction; a regular daily temperature for a long time; gave a positive reaction three months after return; tuberculosis.

Monkeys dying from tuberculosis in the monkey house were as follows:

Drill, No. 6, passed on good forty-eight-hour temperature, died in monkey house eight months afterward of tuberculosis.

Anubis baboon, No. 34, passed on good forty-eight-hour temperature; on exhibition sixteen months; returned and killed; tuberculosis.

Common macaque, No. 205, passed on twenty-four-hour temperature; on exhibition three months; returned; irregular; forty-eight-hour temperature; tuberculosis.

Sooty mangabey, No. 59, passed on good twenty-four-hour temperature, then on forty-eight-hour temperature; after twenty months on exhibition died of tuberculosis. (Traceable to five days' exposure to sooty mangabeys Nos. 60, 62 and 63.)

Grivet monkey, No. 8, passed on twenty-four-hour temperature; one month on exhibition; returned, tuberculosis.

The following is the list of monkeys which were tested early in our work. Their temperature was taken after the injection for only twenty-four hours. Of these fourteen monkeys six died of tuberculosis, some of which were included in the above lists. Seven of the fourteen were retested on the basis of a forty-eight hour temperature after injection, and six of these were negative to the test, while the remaining one gave a positive reaction. This determined for us the necessity of taking the temperature for forty-eight hours at least following the injection.

PASSED ON TWENTY-FOUR-HOUR TEMPERATURE

C—3, Aug. 15, 1905, remaining
A—3, Aug. 15, 1905, remaining
B—4, Aug. 31, 1905, remaining
B—5, Aug. 31, 1905, remaining

} Retested at monkey House, forty-eight-hour temperature, Passed.

Have been at the monkey house three years one month since passing twenty-four hour test.

DIED, NOT TUBERCULOUS

B—3, passed on twenty-four-hour temperature; retested at monkey house, forty-eight-hour temperature and passed; on exhibition two years, five months; died, not tuberculous.

I—1, passed on twenty-four-hour temperature; retested at monkey house, forty-eight-hour temperature, repassed; on exhibition one year, ten months; died, not tuberculous.

I—4, passed on twenty-four-hour temperature; on exhibition two months; died, not tuberculous.

A—26, passed on twenty-four-hour temperature; on exhibition twenty-one days; died, not tuberculous.

DIED, TUBERCULOUS

B—2, tested, twenty-four-hour temperature; died, general tuberculosis.

A—2, tested, twenty-four-hour temperature; died, general tuberculosis.

A—4, passed, twenty-four-hour temperature; died, tuberculous.

A—6, tested, twenty-four-hour temperature; died, general tuberculosis.
C—7, tested, twenty-four-hour temperature; died, general tuberculosis.
I—2, passed, twenty-four-hour temperature; retested at monkey house; returned on forty-eight-hour temperature; again tested (forty-eight-hour); killed; general tuberculosis.

CONCLUSIONS

1. Tuberculosis is a disease which causes a considerable mortality among monkeys. The habits of the animals, moreover, facilitate the transmission of the disease when many are together on exhibition.

2. The primary object of this work was to protect the healthy monkeys by separation of the infected ones. It was therefore diagnostic work, and the use of tuberculin for therapeutic purposes was not tried.

3. It is not possible to trace the source of infection; whether from human beings or from the lower animals. From the number of monkeys that were condemned on the first test it is evident that a large percentage are affected while in the hands of the dealers.

4. To insure the protection afforded by the test, the exhibition house must be freed of infected animals, disinfected, and only non-tuberculous monkeys admitted. The monkeys on exhibition should be retested at least once a year and doubtful animals removed from the cages.

5. To apply the test scientifically a thorough familiarity with the normal temperature of the monkeys is necessary.

6. The normal temperature of the monkey is higher than that of the human being by 4 to 5 F. at its highest point. It follows a regular curve during the twenty-four hours, with the high point at 3 p. m. in the neighborhood of 101 to 102 F.; its lowest level, about 99 F., at 3 a. m.

7. An injection of tuberculin into a non-infected monkey will not disturb the rhythm of the normal temperature.

8. An injection of tuberculin into an infected monkey will cause a definite rise in temperature, a destruction of the daily curve, the performance of a course higher than the daily temperature at the previous high point, or any or all of these.

9. By the test we have been able to detect tuberculosis in 37 per cent. of 128 monkeys tested.

10. No monkey which has passed the test—i. e., given a negative reaction since February, 1906—has shown as yet any evidence of tuberculosis, although some have died from other causes and others have been killed upon suspicion.

11. Ten of the 79 monkeys which were passed were subsequently found tuberculous, either in the exhibition cages or after having been

returned to the laboratory for any reason. These infections are probably traceable to two monkeys which passed the test because of a misinterpretation of their temperature after injection during our early work.

12. By careful consideration of the temperature; by rigid adherence to hygienic measures in quarantine, and by observation of the individual peculiarities of the animals, the tuberculin test will prove an efficient means of separating infected monkeys and preserving exhibition collections.

These investigations here reported were made possible by the broad-minded interest and co-operation of the directors of the Zoological Society of Philadelphia; and we wish to acknowledge with thanks the assistance of Dr. Arthur Erwin Brown, secretary of the society, in our work.

Since the writing of this article six months have elapsed and the statements herein still hold good. It has now been eighteen months since the last monkey on exhibition died of tuberculosis. This monkey was exposed to a tuberculous monkey which passed the early test, before the delayed reactions or the night drop in the temperatures were thoroughly understood. No monkey has been returned for a retest from the exhibition cages or having died of other causes has been found tuberculous of the monkeys tested since February, 1906, or in the past thirty-eight months.

The results of the above methods of testing monkeys and of placing healthy monkeys under good hygienic surroundings for exhibition purposes demonstrates the great value of such tests as the tuberculin test and further gives a very practical lesson in preventive medicine when ideal conditions are offered.

1808 Diamond Street—4443 Spruce Street.

THE RELATION OF HYPERSUSCEPTIBILITY TO IMMUNITY*

PAUL A. LEWIS, M.D.
NEW YORK

The circumstance that the repeated treatment of animals with certain substances, by appropriate methods, tends to establish a state of specifically decreased tolerance for those substances has attracted much attention within the last two or three years. The problems which arise when it is attempted to account for this phenomenon or to make practical use of its specific character have been attacked in most of the laboratories concerned in research in the field of immunity, and in at least two purely physiological laboratories. Not the least interesting and important of these problems concerns the relation which may or may not exist between this phenomenon of specifically decreased resistance and the increased resistance or immunity which is so often obtained when toxins, bacterial products or living bacteria are repeatedly given to an animal in suitable fashion. The contrast between the two conditions is self-evident, and while, as our knowledge of the two sets of phenomena has been developed, attention has been largely centered on the condition of increased tolerance, writers have not been wanting who have seen in the state of hypersusceptibility a condition which in certain instances, at least, might underlie the immune state. It is my present purpose to present briefly some observations bearing on points in this discussion and to restate, also in brief, some of the views already expressed in respect to the relationship between anaphylaxis or hypersusceptibility and increased tolerance or immunity. In order that the close of my paper may not bring with it a feeling that the promise of a title perhaps too comprehensive has been poorly kept, I may state in the beginning that I am unable to offer conclusive evidence either for or against there being a general interdependence of the two sets of phenomena and that my only hope is to show that a ripened judgment on these matters is not possible until further facts are at our command.

A few words as to terminology: It has been a common practice in recent years to speak of any reaction of the animal organism to foreign substances in the course of which antibodies are formed as an immunity reaction and, concomitantly, of the treated animal as immune, even

* From the Laboratories of the Rockefeller Institute for Medical Research.

when the foreign substance was not in itself demonstrably harmful. For the animal once treated with a substance capable of calling forth the production of antibodies it seems less confusing to adopt the more general term proposed by v. Pirquet[1] and to say that the animal is in a state of "allergy," meaning a state in which the potentiality for reaction to that particular substance is altered. We are not thereby committed to any increase in tolerance. Induced hypersusceptibility and induced tolerance are thus, by definition, types of allergy. The reactions of hypersusceptibility most studied of late have been those in which relatively non-toxic proteid substances such as blood serum and egg-white have been employed. The toxic phase, at least, of these reactions is characterized by a symptom-complex which is almost if not quite unique, and which varies more in character with the species of animal worked with than with the particular substance employed. For this newer, well-characterized condition the word "anaphylaxis" is now most generally employed and is sufficiently expressive.

In the toxic phase of the reaction of anaphylaxis, it will be recalled, the animal exhibits marked disturbance within a few minutes after the injection. Death may occur in from two to five minutes if the injection has been given into the circulation or into the cerebrospinal cavity. If the animal survives for six hours it almost always rapidly recovers. Convulsions are often a prominant feature of the reaction. In the rabbit, where the toxic phase is evidenced by necrosis when the test injection is made subcutaneously, this necrosis always occurs at the site of the test injection rather than at the site of previous injections.

A specifically decreased tolerance is the important feature of the tuberculin reaction. But the tuberculin reaction is very different in important particulars from the reaction of anaphylaxis to serum. The tuberculous animal treated with tuberculin, even if a large injection is given directly into the circulation, shows no symptoms for a considerable time, and seldom if ever in less than six hours. The animal may die even after twenty-four or forty-eight hours. When a local reaction results from a tuberculin injection it occurs at the site of the foci of disease rather than at the point of the injection of the tuberculin. These distinctions in point of fact, it would seem better to maintain in terminology, and I shall therefore speak of the tuberculin reaction as a reaction of hypersusceptibility rather than as an instance of anaphylaxis. The point of these remarks will become apparent in connection with the following experiments with tuberculin:

1. v. Pirquet, C.: Die Serumkrankheit, Vienna, 1905.

I. TUBERCULIN HYPERSUSCEPTIBILITY AND ANAPHYLAXIS

It can hardly be doubted that tuberculin hypersusceptibility bears some relation to immunity against the *Bacillus tuberculosis*. Such an authority as Trudeau[2] has, however, very recently stated that he is in doubt as to the exact part which the condition of tuberculin hypersusceptibility plays in immunity to the micro-organism. One of the first points to arise when this question is considered is whether hypersusceptibility can be induced with the "pure tuberculin," a hypothetical constituent of tubercle bacilli, contained also in various extracts of the bacilli. Attempts to render animals hypersusceptible to extract-preparations apart from the bodies of the bacilli had, until recently, failed entirely. Calmette[3] and his assistants, however, were able to render calves hypersusceptible to a preparation of Koch's old tuberculin purified and concentrated by alcoholic precipitation. It has been assumed that this success depended on the presence of the "pure tuberculin." I have recently carried out similar experiments, using an analogous tuberculin preparation, prepared by Dr. Levene, and the guinea-pig as the animal for experiment.

Four animals were treated with 10 mg. of this preparation subcutaneously. A second treatment with the same quantity injected into the heart after two weeks gave no reaction. A third treatment with 10 mg., introduced into the heart four weeks later, gave a very slight immediate reaction. Two weeks later—that is, two months after the first treatment—the animals were given 10 mg. intracardially. They gave now severe immediate reactions corresponding perfectly in character to serum anaphylaxis. One of the animals died in about five minutes. Those which did not die recovered fully in four or six hours.

As a control experiment, I concentrated two liters of 5 per cent. glycerin bouillon to 200 c.c. and precipitated twice with 60 per cent. alcohol, a procedure comparable to that by which the tuberculin preparation was made. The precipitate obtained was not quantitatively comparable, however, to the tuberculin because of the presence of inorganic salts. Nevertheless, 10 and 20 mg. of this precipitate, doses entirely without action on normal guinea-pigs, gave sharp reactions of anaphylaxis with the surviving animals of the previous experiment.

In these experiments, which were also controlled by others in which animals treated with living and dead tubercle bacilli were injected with the same dose of tuberculin, it was apparent that one had to do, not with the tuberculin reaction, but with the reaction of anaphylaxis in the restricted sense in which the term was used above. It seems possible that such results as Calmette's[3] might be due in some measure to bouillon

2. Trudeau, E. L.: Antibacterial or antitoxic immunization in tuberculin treatment. Jour. Am. Med. Assn., 1909, lii, 261.

3. Calmette, A.: International Congress on Tuberculosis, Washington, 1908.

constituents.[4] The question as to whether the "pure tuberculin" sensitized as well as intoxicated is therefore still an entirely open one so far as experiment goes.

II. THE RELATION OF HYPERSUSCEPTIBILITY TO ANTITOXIC IMMUNITY

What is known of reactions of hypersusceptibility to the true toxins was developed some years before the beginning of the recent systematic study of anaphylaxis. Von Behring and Kitashima[5] in 1901 reported a remarkable experience in connection with attempts to immunize guinea-pigs against diphtheria toxin. They worked on a system which Behring had developed as most efficient in producing the specific antitoxin in horses. This system was to begin with a dose considerably below that needed to produce any symptoms or lesions in the animal and then on each succeeding day to double the dose of the preceding day until a point was reached where severe reactions were obtained. From this point, which in the horse was seldom attained until very large doses of poison had been reached, the dosage was increased more slowly and the treatment given at longer intervals. When an attempt was made to immunize guinea-pigs according to the same scheme it failed in the beginning, and the authors sought to attain their end by initiating the treatment with smaller fractions of the certainly fatal dose—in other words, increasing the time required to reach the point when reactions would normally occur. The results, which are reported in great detail as concerns two series of experiments, were as follows:

Beginning the treatment with 1/400,000 of the minimum fatal dose for guinea-pigs, and, as I have said, doubling the dose each succeeding day, the animals died when they reached the point when about 1/700 of a certainly fatal dose had been given as a maximum and when the total amount of diphtheria toxin given was but 1/400 of that required to kill when given at one treatment. The protocols of some such animals are

4. These experiments obviously have an important bearing on the subject of anaphylaxis with simple proteids. The preparations of tuberculin and bouillon precipitate were boiled a number of hours in the process of concentration and precipitated repeatedly with alcohol. The bouillon used in making the control preparation had been sterilized in the autoclave at 110 C. for fifteen minutes before the concentration was begun. That used in the preparation of the tuberculin had probably been subjected to the same process when made. Both the "sensitizing" and "intoxicating" factors in these preparations were therefore thermostabile as against prolonged exposure to a temperature of 100 C. in contact with glycerinated water. Presumably they had withstood as well a short exposure to a higher temperature.

5. von Behring and Kitashima: Ueber Verminderung und Steigerung der ererbten Giftemfindlichkeit. Berlin klin. Wchnschr., 1901, xxxviii, 157.

given in detail. The authors were evidently convinced that the animals had died of the specific intoxication.

Having it in mind that in these experiments as reported there had not been excluded the possibility of there being a simple although extreme case of accumulation, and that, in view of the theoretical importance of the question, it would be well to see if it would be possible to vary the condition in such a way as to bring out any relation to the reaction of anaphylaxis as we know it now, I undertook to repeat the observations.

Six large guinea-pigs (the size used by von Behring and Kitashima) were chosen, and, beginning with 1/100,000 of the minimum fatal dose, they were treated according to the system described. After the third dose (1/25,000 of the minimum fatal dose) one of the animals died of a paracolon septicemia. After the fifth dose it was noticed that a second animal, which had had a small patch of mange, was somewhat thin and that the skin lesion had extended very rapidly. It seemed proper to discard this animal. The four remaining animals lost some weight for the first ten days but regained this in succeeding days as the treatment was continued. They all maintained weight and health until two-fifths of the minimum fatal dose had been given as a maximum. On the next day it was found that one of the four had lost 30 gm. weight in the twenty-four hours. This animal was not further treated. It lost more weight, suffered a slight paralysis in the third week and finally recovered fully. The three remaining animals received four-fifths of the minimum fatal dose on this day. One of them was dead in twenty-four hours with the typical picture of diphtheria intoxication. The other two were sick and were not further treated. One died of paralysis at the end of the second week, the second suffered severe paralysis and emaciation but made a recovery. When it is recalled that the minimum fatal dose of the toxin is the dose which kills in from three to five days, that large guinea-pigs are somewhat less definite in their normal susceptibility to the toxin than small ones, and that in this experiment the three animals which went through to the end received seven-fifths of the minimum fatal dose in three days, it does not seem that the result is other than would agree with the view that the animals had reacted in a normal way and that the earlier treatments with the small fractions of a fatal dose had exerted no appreciable influence on the result.

Having in mind the factor of lapse of time, or incubation period so important in the instances of true anaphylaxis, the experiment was repeated with certain variations.

Young animals were chosen. The starting point was again 1/100,000 of the minimum fatal dose. All were treated by doubling the dose each day until a maximum of 1/800 of the minimum fatal dose was reached. This it will be recalled was the point at which the reaction was obtained by von Behring and Kitashima. Up to this point the animals were normal in activity and gained steadily in weight. In the case of three of the series the treatment was continued until 1/25 of the minimum fatal dose was reached. Weight and activity were maintained, although growth was perhaps somewhat less rapid toward the last. The hair fell out over the site of the last few injections also. The experiment along the original lines was now interrupted, as it seemed to be following in the wake of the first series.

Four days after the last injection of the series two of these animals with a control were injected with one hundred fatal doses of toxin. One subcutaneously,

the second by the intracardiac route. A control was also injected into the heart. The animal treated subcutaneously was entirely well for six hours and was found dead the next morning. The animals injected into the heart seemed slightly indisposed during the first six hours and were dead the next morning.

The three animals in which treatment had been stopped at 1/800 of the minimum fatal dose were tested, one at ten days, and two at two weeks, after the last injection with single minimum fatal dose of the toxin and found to react as normal animals.

To the above experiment may be added the result of another in which it was found that young guinea-pigs treated with a rather large dose of washed diphtheria bacilli reacted normally to toxin three weeks later.

It was to be expected that if the preliminary treatment had rendered the animals hypersusceptible to the toxin as such, it would show itself in a shortening of the incubation period of the intoxication. There was no evidence of this in the above experiments. Moreover, it is conceivable that the toxin itself might give rise to a reaction of anaphylaxis in its narrower sense. No evidence of such reaction was seen in the animal treated by intracardiac injection. The dosage is such that the possibility of producing the reaction of anaphylaxis with the unused non-specific peptone constituents of the crude toxin is not excluded.

It is not, of course, possible on the basis of these experiments to discredit the observations of von Behring and Kitashima. But one can, I think, safely conclude that the phenomenon is not a general one on which far-reaching conclusions can be based. One might find in some inconstant constituent of the crude toxin, or in some abnormal condition of the guinea-pigs used, an adequate explanation for the phenomenon if the experiments were conducted on a larger scale and with a mind open to the various possibilities suggested by the recent work on anaphylaxis. Diphtheria toxin is a substance of such stable qualities that it is unlikely that an experiment of this striking character should fail to give constant results if it depended on the toxin itself.

The chief further evidence in the literature bearing on the question of hypersusceptibility to diphtheria toxin concerns the reaction of horses. These animals in the course of immunization occasionally break down, the effect of further treatment being to cause serious illness or death. The antitoxin content of the blood of these animals in the stage of intoxication or at death is often lower than previously, but is most frequently still very high. This state of affairs, known as "the paradoxical phenomenon of Kretz," is a paradox only in virtue of the assumption that it is the toxin itself which kills the animal. Of this there is no direct evidence and much may be said against making the assumption. Horses continuously treated with bacteria or bacterial products of other kinds—streptococci, typhoid bacilli, etc.—show the same phenomenon

and at autopsy present the same lesions. These lesions, amyloid liver, hemorrhage within and about the liver and a large amount of bloody fluid in the peritoneal cavity, are not those characteristic of the acute intoxication with diphtheria toxin; and I know of no evidence drawn from work with horses which indicates a specific hypersusceptibility to diphtheria toxin. Moreover, it may be doubted if it is proper to speak of this condition in the horse as one of hypersusceptibility in our sense of the word. While the animals at the end are, without doubt, less able to withstand treatment than at the highest point of the immune state, yet they will take without difficulty many times the dose which would kill a normal animal. They are also, by reason of anatomical alterations, fully as liable to die in this particular way after being bled as they are after being treated with the product with which they are immunized.

Knorr[6] also presented, from von Behring's laboratory, evidence in kind similar to that I have reviewed for diphtheria toxin, for a specific hypersusceptibility to tetanus toxin. Loewi and Meyer[7] in going over the work recently find that they are able to explain the reactions of Knorr on the supposition that there is in this case an absorption of tetanus toxin along the nerves and a gradual diffusion throughout the central nervous system and a very slow elimination. Subsequent injections find the susceptible cells hypersusceptible, but only because of the presence of the specific substance in them; hence a peculiar case of accumulation. Whether this be the true explanation or not, they do show rather clearly that the reaction has nothing to do with the production of the specific antitoxin.

Doerr and Raubitschek[8] compared the effects of anti-ichthyotoxin (anti-eel-serum) as a neutralizing substance for the toxin and as an agent in the passive transfer of serum anaphylaxis. They were able to show that the two properties of the antiserum were independent of one another. These results could be amplified to show that the eel serum contains a native toxin of specific action quite independently of the substances which give rise to a serum anaphylaxis fully comparable to that produced by the non-toxic sera. There is no evidence that it is possible to produce a state of specific hypersusceptibility to the native ichthyotoxin.

In summing up we may safely say, I think, that there is very little evidence for a specific hypersusceptibility to the true toxins or conse-

6. Knorr: Habilitationsschrift, Marburg, 1895. (This publication is not accessible; von Behring repeatedly cites this work in the present connection.)

7. Loewi and Meyer: Tetanus-Gift Empfindlichkeit und Weberempfindlichkeit. Arch. f. Exper. Path. u. Pharmakol., 1908, lix, 355.

8. Doerr, R., and Raubitschek, H.: Toxin und Anaphylactesurende Substanz des Aal-Serums. Berlin klin. Wchnschr., 1908, xlv, 1525.

quently for the regular occurrence of a state of specific hypersusceptibility as a condition underlying antitoxic immunity.

III. ANTIENDOTOXIC, OR ANTIBACTERIAL IMMUNITY

In a large group of diseases the causative micro-organisms have never been made to produce a characteristic extracellular poison in artificial cultures, the intracellular poisons or endotoxins being commonly held responsible for the activity of the bacteria as disease producers. Our methods of obtaining these hypothetical endotoxins are very imperfect. In a few instances active poisons of well-defined activity have been obtained by autolysis of the culture, or by grinding or dissolving the cultures. It has also been shown by various observers that with a number of these bacteria the phenomena of anaphylaxis can be obtained by treating an animal repeatedly with the living or killed cultures. The latter statement is also true for certain non-pathogenic bacteria. As well as can be judged from the description given by the various writers (and my own limited experience coincides with this), the phenomenon of anaphylaxis with bacterial cultures corresponds exactly with the anaphylaxis to non-poisonous proteids, such as serum and egg-white.

In order to assign to the phenomenon of anaphylaxis in the narrower sense a fundamental place in the immunity to diseases of the type of typhoid fever, cholera or the septicemias and localized diseases due to micrococci, it would seem necessary to assume that the disease is due to the bacterial proteid as such. This assumption was indeed made by Wolf[9] in 1904. This author believes that endotoxin and bacterial proteid are identical. This assumption would seem contrary to the general fact that the diseases caused by these bacteria are entirely distinct in their manifestations, that each is well characterized in its symptomatology, lesions and duration. It seems much more probable that the bacterial substance is largely made up of indifferent proteid which must of course be carried into the body when the bacteria enter as invaders, and that the processes resulting in the reaction of anaphylaxis are concerned in removing this relatively indifferent or non-toxic proteid.

Whether or not hypersusceptibility can be induced against the toxic autolysates or extracts of bacteria of this class, which are perhaps the nearest approach to the endotoxins with which we are able to deal, is as yet an open question.

It has, however, been shown by a number of investigators that processes which seem fitted to render an animal immune to bacteria of this

9. Wolf, A.: Ueber Grundgesetze der Immunität. Centralbl. f. Bakteriol. u. Parasitenk., 1904, xxxiv, 390.

class may, if not perfectly co-ordinated, result in an apparent hypersusceptibility. Thus the well-known process of bacteriolysis may be exaggerated as an independent phenomenon to such degree that an overwhelming amount of poison is suddenly set free and the treated animal dies more quickly and certainly than control animals infected with the same quantity of bacteria. This phenomenon, whether brought about as a passive or an active process, must be considered as an imperfect development of a complex immunity reaction in which the mechanism for disposing of the endotoxin is poorly developed in comparison with that for destroying the life of the bacteria.

The phenomena of anaphylaxis must of course complicate this process, as the bacterial proteid is always present under these conditions. It cannot be denied that the anaphylaxis may influence the final result either in a favorable or an unfavorable way—unfavorable because the presence of a possible second intoxication side by side with the first may intensify the reaction. If, moreover, the anaphylactic reaction were mild and soon over, the establishment of a partial or complete refractory state which occurs so promptly might influence favorably in a non-specific way the reaction to the true endotoxin. It was shown long ago by Wehrman[10] that animals treated with non-fatal doses of eel-serum became in a few hours considerably more resistant, not only to eel-serum, but to snake-venom. The refractory state of proteid anaphylaxis, as was shown by Gay and Southard, is only relatively specific, working in such a way that an animal rendered refractory to the more intense reactions was refractory as well to the weaker ones. The processes, however complex they may be and however impossible it may be at present to keep them separate in experiment, must be considered separately if we are to avoid a hopeless confusion in work and ideas.

Whatever our opinion as to the place of toxin or endotoxin hypersusceptibility in relation to effective immunity, it seems clear that the reaction of anaphylaxis to proteids is an instance of allergy comparable in value to bacteriolysis, agglutinin or precipitin formation. In its place it seems to have most in common with the phenomenon of specific precipitin formation. It concerns the same class of substance. The first thought of some was that the intoxication in anaphylaxis was due to intravascular precipitin formation. This was soon shown not to be the case. Pick and Yamanouchi[11] have recently shown, however, that a

10. Wehrman: Recherches sur les propriétés toxique et antitoxique der sang et due bile des anguilles et des vipères. Ann. de l'Inst. Pasteur, 1897, xi, 8111.

11. Pick and Yamanouchi: Chemische und Experimentelle Beiträge Zum Studium der Anaphylaxie. Ztschr. f. Immunitätsforsch, 1909, i, 676.

serum containing specific precipitin is capable of calling forth the anaphylactic reaction when injected into an animal sensitized with the same proteid as antigen, an observation suggesting some close relation between the two reactions, although further investigations might show that in this instance also the relation was one of coincidence rather than of fundamental association.

To sum up, I would say:

1. The evidence that there exists a condition of specific hypersusceptibility to the true toxins, such as diphtheria and tetanus toxin, as an underlying factor in antitoxic immunity, is not at all convincing.

2. Processes, such as bacteriolysis, which seem to be of fundamental importance in the state of immunity against certain bacteria, may, if exaggerated, give rise to an apparent hypersusceptibility which is really an imperfect immunity. There is no good evidence for the occurrence of a specific hypersusceptibility to endotoxins. The questions involved are rendered still more complicated by the fact that the phenomenon of anaphylaxis may be developed with bacterial proteids which are probably not in themselves factors in the production of disease.

3. The results of experiments which have been supposed to show that specific hypersusceptibility can be induced against the hypothetical "pure tuberculin" are so complicated by the presence of admixed substances that no final conclusion can be drawn from them. These admixed substances, presumably thermostabile bouillon constituents, may under suitable conditions give rise to a typical reaction of anaphylaxis.

The Rockefeller Institute for Medical Research, 66th Street and Avenue A.

PROTEIN METABOLISM IN TYPHOID FEVER*

PHILIP A. SHAFFER, PH.D., AND WARREN COLEMAN, M.D.

WITH THE ASSISTANCE OF

MICHAEL SOMOGYI, E. A. REINOSO AND EDNA CUTLER

NEW YORK

It has long been known that during the febrile reaction to acute infections the katabolism of protein is intensified, resulting in an increased excretion of nitrogenous substances in the urine. This phenomenon is of such constant occurrence that it may properly be considered a characteristic of fever.

Because of this increased katabolism and of the disproportion between the anabolism and katabolism of protein the subject becomes poorer in nitrogenous substances. After the termination of the disease the protein katabolism falls in intensity to or even below the normal limit, the anabolic process becomes more prominent, and during this reverse disproportion between the processes of assimilation and destruction the organism repairs its losses of protein and other substances.

These conditions, fever and convalescence, afford two of the most interesting fields for the investigation of the complicated principles of physiological and pathological nutrition, as has been demonstrated by the numerous papers on these subjects.

During the past two years we have been engaged in a study of the protein metabolism in typhoid fever. The main object of the investigation was a study of certain aspects of the febrile katabolism of body protein. We hoped to determine to what extent, if at all, the loss of body protein during the disease could be prevented or retarded by different forms of food, and to establish the physiological characters of the diets best suited for this purpose. The experiments to be reported concern chiefly the effect of diets rich in carbohydrate. We have also accumulated much material concerning the quantitative composition of the urine from which we hoped some further knowledge might be obtained of the degree of abnormality in the intermediary metabolism of nitrogenous substances in this disease.

* From the Laboratory of Pathological Chemistry, Department of Experimental Pathology, Cornell University Medical College, and the Second Medical Division of Bellevue Hospital, New York City.

For a critical review of the extensive literature relating to the metabolism in fever and allied subjects the reader is referred to various papers, especially that by Kraus, in von Noorden's "Handbuch der Pathologie des Stoffwechsels." We shall cite in the following pages only a few of the papers having an immediate bearing on our experiments.

THE LOSS OF BODY PROTEIN

The loss of body protein, calculated from the minus balance of nitrogen, is very great in typhoid fever. F. Müller's patient who lost 86.4 gm. of body nitrogen, the equivalent of 2.5 kg. of muscle tissue, in eight days is not very unusual. In an experiment reported by Leyden and Klemperer[2] the subject lost 109.4 gm. of body nitrogen, the equivalent of 3.2 kg. muscle tissue, in twelve days. In neither instance do the figures given represent by any means the total loss of body protein during the whole course of the disease in these patients. The loss for short periods is often relatively much greater, a loss of 15 to 20 gm. nitrogen per day not being very unusual in the early stages of severe attacks in muscular individuals.

This loss of body protein, which apparently occurs during all acute infectious fevers, is due both to an increased destruction and to a decrease in the regenerative processes, both changes serving to intensify the disproportion between the anabolism and katabolism of protein.

The increased katabolism is at present generally believed to be due to at least two fairly distinct causes: to the pyrexia itself and to the action of bacterial toxins on the body cells or fluids, quite apart from the pyrexia. The decrease in the anabolism, the regenerative processes, is largely the result of a lowered or insufficient food-supply; the latter point may be better appreciated after considering the factors involved in the febrile katabolism.

EFFECT OF SIMPLE PYREXIA

An artificial raising of the body temperature above the normal for some hours results in an increased katabolism of protein. Fritz Voit[3] observed that, if the temperature of a fasting dog was raised to 40 or 41 C., the nitrogen excretion was increased about 37 per cent. This increase was obtained only after maintaining the higher temperature for twelve hours, and Voit concluded that the increase of protein metabolism

1. Müller: Centralbl. f. klin. Med., 1884, v, 596.
2. Leyden and Klemperer: von Leyden's Handbuch der Ernährungstherapie, 1904, ii, 345.
3. Voit, F.: Sitzungsb. d. Gesellsch. f. Morphol. u. Physiol. in München. 1895, xi, 120.

took place after the greater part of the store of glycogen had been exhausted. Schleich,[4] Linser and Schmid,[5] and others have performed similar experiments. Schleich found the urea excretion of a man to be noticeably increased on raising the body temperature for several hours by means of hot baths to 39.5 C. Linser and Schmid found an increase of protein metabolism on raising the body temperature of a normal man, as well as of a subject of ichthyosis hystrix, above 39 or 40 C. The last-mentioned investigators believe that a simple pyrexia causes an increase in the protein metabolism only when the temperature is above 39 C. (102 F). It appears, therefore, that the febrile temperature in typhoid fever may be one of the factors which increase the protein metabolism.

THE EFFECT OF TOXINS

The human subject of an infectious fever excretes, during the height of the disease, much more nitrogen in his urine than does either a starving man or a man whose body temperature has been raised by artificial means. The same rule holds true for animals experimentally infected with pathogenic organisms or injected with bacterial toxins.

Neither simple pyrexia nor the degree of starvation alone is sufficient to explain the whole of the increase in protein katabolism, and it becomes necessary to seek some further factor which may act in this direction. Most writers call this factor the "toxic" or "toxogenous" destruction, meaning merely the effect of the bacterial toxins on the katabolic processes.

While there seems to be no doubt that the toxins have a distinct part in the cause for the febrile katabolism, the mechanism of this "toxic" action is not known. One hypothesis is represented by the statement of Krehl[6] that it is "very probable that the agent causing the fever actually destroys the cell proteids in various parts of the body." According to this idea the increase in febrile katabolism involves only protein.

Benedict and Surányi,[7] on the other hand, deny the existence of this sort of a toxic destruction, believing that the increased protein katabolism is merely a part of an increase in the total metabolism which Aronsohn[8] believes may be caused by the action of toxins on either enzymes or the nervous mechanism controlling the consumption of food and body materials.

---

4. Schleich: Arch. f. exper. Path. u. Pharmakol., 1875, iv, 82.
5. Linser and Schmid: Arch. f. klin. Med., 1904, lxxix, 514.
6. Krehl: The principles of clinical pathology, Philadelphia, 1905, p. 394; transl. by Hewlett from 3rd German ed.
7. Benedict and Surányi: Ztschr. f. klin. Med., 1903, xlix, 502.
8. Aronsohn: Ztschr. f. klin. Med., 1907, lxi, 153.

Krehl's view of the toxic destruction appears to be supported by the results of May,[9] who studied the total metabolism in fasting rabbits infected with hog cholera and found a marked increase in protein katabolism, but no increase in the consumption of fat; though May concluded from his experiments that the increased protein destruction was chiefly the result of an insufficient carbohydrate supply.

Stähelin,[10] on the other hand, working with a dog infected with surra, found an increase in the consumption of fat as well as protein, thus indicating that non-nitrogenous substances also take part in the increase of febrile katabolism.

PARTIAL STARVATION

If a subject does not receive food of a sufficient caloric value to meet the daily energy exchange, his body material is drawn on to supply the deficit. This factor is responsible, in most cases of typhoid fever, for a part of the loss of body protein. The caloric value of the diets now used in the disease is lower than would maintain equilibrium in even a normal subject, with the result that there is not only a decrease in the anabolic processes, but the body tissues or fluids are further drawn on for an additional supply of energy.

The degree of this partial starvation and the amount of the contingent (starvation) loss of body protein is determined both by the food intake and by the total requirement for energy. No satisfactory general estimate of the amount of the latter factor can be made at present; it will vary greatly with different subjects and at different stages of the disease.

It is certain that the energy requirement of such subjects is not lower than the normal (about 33 cal. per kilo[11]), but we cannot predict how much greater it is than the normal in any individual case unless we know the extent of the febrile increase in total katabolism. According to Krehl,[12] the febrile increase in heat production varies between 10 per cent. and 60 per cent.; the latter estimate would give a requirement of about 53 cal. per kg.

---

9. May: Ztschr. f. Biol., 1894, xxx, 1.

10. Stähelin: Arch f. Hyg., 1904, L, 77.

11. At ordinary rest the heat production of a normal fasting individual is about 30 cal. per kg. body weight. The heat production at complete rest is lower than this, Johannson recording about 22 and Atwater, in an experiment during sleep, 22.8 cal. per kg. Typhoid patients are, however, rarely at complete rest; the restless movements in bed and the shivering after frequent "tubs" or sponges appear sufficient to justify accepting at least 30 cal. per kg. as the basis for this calculation. To this starvation requirement we must add 10 per cent. to allow for the dynamic stimulation of metabolism caused by food (Rubner.)

12. Krehl: The Principles of Clinical Pathology, Philadelphia, p. 382.

We have attempted above to outline the factors, so far as they are at present known, which are responsible for the febrile loss of body protein. We have seen that the increased katabolism of body protein is due on the one hand to the febrile temperature of the subject and on the other to the action of bacterial toxins; and that this katabolism may be, and usually is, further increased by an inadequate food-supply and the consequent burning of body material as a source of energy. What are the possibilities of retarding the protein katabolism by dietetic means? It is obvious that the increased katabolism of body materials and the loss of body protein due to simple starvation may be prevented by sufficient food.

And if the view held by Benedict and Surányi, Aronsohn, and in a qualified form by May[13] be true, that the effect of the pyrexia and of the action of toxins is merely an increase in the total katabolism, resulting in a greater demand for energy-producing material, the situation with these factors also becomes one of undernourishment. The body protein, together with fat, is drawn on as in simple starvation to meet the demand for fuel, though in larger amounts on account of the increased heat production. The chief obstacle to this view has been the apparent impossibility of preventing a loss of body nitrogen in a fever subject, even though he be given food of such caloric value as supposedly to cover his energy exchange; and the lack of success in such efforts is, in fact, largely responsible for the conception of a "toxic" destruction of body protein, in the meaning of Krehl. But, according to our experiments, the reason for this lack of success is not that it is impossible to prevent this febrile loss of body protein, as would be the case were Krehl's conception true, but that food of sufficient fuel value and of suitable character has not been used.

Voit, and Linser and Schmid, were able to retard the increased protein katabolism of simple pyrexia by giving additional carbohydrate in the food.

To retard or to prevent the excessive katabolism of body protein due to the action of toxins has been found very difficult; the experiments of Weber[14] are the only ones in which success is clearly shown. This investigator injected extract of glanders bacilli into a sheep and obtained a loss of nitrogen, although the animal received a diet which had previously maintained nitrogen equilibrium. In a second experiment, with food equivalent to 73 cal. per kg., the animal gained nitrogen during six days of fever. The gain, however, was less than during the normal

13. May: Ott: Chemische Pathologie der Tuberculose, Berlin, 1903, p. 259.
14. Weber: Arch. f. exper. Path. u. Pharmakol., 1901, xlvii, 19.

periods. He was able, therefore, wholly to prevent a loss of body protein which, with less food, would have been caused both by the pyrexia and by the direct action of the toxins on the protein metabolism.

In a subject of typhoid or other infectious fever it is difficult, and usually impossible, to study the effect singly of partial starvation, pyrexia, or the action of toxins on the protein katabolism, and one must ordinarily be content with determining the combined effect. This is essentially what has been done by Weber, by May with rabbits, and by Puritz,[15] and Leyden and Klemperer, with human subjects of typhoid fever.

All these experiments give some indication, it seems to us, that the total protein katabolism in fever, and the loss of body protein, may be influenced by the caloric value of the food. May and Weber drew this conclusion from their experiments, but the principle involved does not appear to have been accepted as generally applicable, and the results of these experiments have had no effect upon the dietetic treatment of febrile conditions in the human subject. Puritz believed the loss of body protein to be less with high protein diets; Leyden and Klemperer, though of the same opinion, conclude that the "toxic" loss of protein cannot be affected by any dietary régime.

There are other reasons for believing that food of high caloric value and especially rich in carbohydrate should be effective in protecting the body protein from excessive destruction in fever. The work of Lusk,[16] Sivén,[17] Landergren,[18] Folin,[19] Murlin,[20] and others has shown the superior value of carbohydrate in sparing body protein in afebrile conditions.

Fat alone fed to an animal retards the loss of body protein little or not at all, but spares an equivalent quantity of body fat.[21]

Protein when alone must be given in extremely large amount before nitrogen equilibrium is obtained, because of the large specific dynamic effect (Rubner) of protein in increasing the total metabolism. Carbohydrate alone, on the other hand, may reduce the amount of nitrogen excreted by 50 per cent. to 70 per cent. of the starvation excretion.

Our experiments were undertaken with the hope, based on the considerations stated in the preceding pages, that the total febrile destruc-

15. Puritz: Virchow's Arch. f. path. Anat., 1893, cxxxi, 327.
16. Lusk. Ztschr. f. Biol., 1891, xxvii, 459.
17. Sivén: Skand. Arch. f. Physiol., 1901, xi, 308.
18. Landergren: Skand. Arch. f. Physiol., 1903, xiv, 112.
19. Folin, Otto: Am. Jour. Physiol., 1905, xiii, 66.
20. Murlin: Am. Jour. Physiol., 1907, xx, 234.
21. A portion of the carbohydrate of a maintenance diet may be replaced by fat without materially affecting the protein katabolism. The above statements refer to previously starved animals.

tion of body protein might be decreased even to normal limits by the addition to the food of large quantities of carbohydrate. It seemed to us probable that carbohydrates might exert the same or similar protecting influence on the body protein during the febrile reaction in man as they do during partial starvation.

These expectations have been realized to the extent that we have found it possible, by giving diets of unusually high caloric value, and consisting principally of carbohydrate, very greatly to diminish and in some instances wholly to prevent the loss of body protein as indicated by the nitrogen balance. Our investigation includes work on twenty-four subjects of typhoid fever, the results from all of which show, with a fair degree of uniformity, though to varying extents, that other factors, such as temperature, intensity of the febrile process, protein intake, etc., being the same or comparable, the loss of body protein becomes less the higher the caloric value of the food. The results from only seven subjects need be given. The results and conclusions from the work with other subjects are in substantial agreement with these.

PLAN OF EXPERIMENTS

The procedure was varied with the different subjects. A constant diet from day to day was frequently impossible, but the amount of food taken in each twenty-four hours was accurately recorded. The protein, fat and carbohydrate, as well as the caloric value of the food, has been calculated from the following data, based in part on our own analyses made from time to time and in part upon König's and Atwater and Bryant's tables.

	Protein	Carbohydrate	Fat
	%	%	%
Milk (by volume)	3.3	5.0	5.0
Cream (by volume	2.0	3.0	30.0
Butter (by weight)	..	..	85.0
Toast	11.0	60.0	..
Eggs (selected to weigh about 60 gm. gross)	12.0	..	9.0
One egg	(7.2 gm.)	..	5.4 gm.)
Lactose	....	100.0	..
"Somatose"	12.4% nitrogen		
Liebig's meat extract	9.2% nitrogen		
Whisky	40.0% alcohol		

The energy value of the diets is calculated on the basis of Rubner's figures:

1 gm. protein ..... 4.1 cal.
1 gm. carbohydrate ..... 4.1 cal.
1 gm. fat ..... 9.3 cal.
Nitrogen × 6.25 = protein.

The urines were collected in twenty-four hour quantities. The collection of complete twenty-four-hour urines from bed patients who are acutely ill is not an easy task, and in a large and busy ward in a general hospital is frequently very difficult. For the success of an investigation of the nature here reported it is necessary that one have every possible assurance, rather than only an assumption, that the urines are complete. During the last half of the work two special nurses, who had no other duties than attendance on the patients being studied, were detailed through the courtesy of Dr. S. T. Armstrong, superintendent of the hospital, and of Miss Goodrich, superintendent of nurses. To the care of these nurses is due the infrequency of the loss of urines as well as the successful and accurate administration of the food.

The following is a form of printed blanks which were written up and signed by the nurses and sent to the laboratory with each bottle of urine or feces:

METABOLISM IN FEVERS

Name .....Ward.....Bed.....

a. m.

Urine for 24 hours, ending at..... (date).....

p. m.

a. m. a. m.

Feces for.....days, from..... .....to..... .....

p. m. p. m.

a. m. a. m.

Temperature: lowest.....at..... .....; highest.....at.....

p. m. p. m.

p.m.

Weight of patient.....lbs. at..... (date).....

a. m.

NURSES:	Quantity of Urine.
.....	

Each nurse, when she goes off duty, will please sign her name above stating the time she was in charge of the patient. If no accidents concerning the administration of food (as refusal to take all or part, or loss of through vomiting—if patient vomits, state hour) or the collection of the *complete excreta* have occurred, she should write O. K. after her name. Otherwise, she should describe on the back of this sheet the amount of food refused or left or vomited, and the approximate quantity of urine or feces lost and how it was lost. Please send this sheet to the laboratory with its corresponding specimen.

When this sheet is used for a specimen of feces, data concerning urine, temperature and weight may be omitted.

By this means responsibility for the collection of excreta and administration of food was centered on individuals, with the result that accidents of this nature were rare, and, more important still, were accurately recorded when they did occur.[22]

22. A similar blank had been previously used by Folin and one of us (Shaffer) at the McLean Hospital. Printed blanks also were used daily for recording in the ward the amount and kind of food taken by each patient. To the advantages derived from the use of these blanks we attribute in large measure the technical success of our experiments.

The urines were analyzed at once for total nitrogen, kreatinin, kreatin, and in many instances for other substances. In some cases "composites" representing a number of days, were made by mixing aliquot parts of consecutive urines. These composites were then analyzed for the substances stated in the tables.

The feces, marked off by charcoal, were collected and analyzed for total nitrogen during a part of some experiments, but not in all. It is to be regretted that the limited capacity of the laboratory prevented further work on the feces. For the calculation of the nitrogen balance we have used nitrogen figures for each day's urine, and, except where the feces were analyzed, have arbitrarily taken 15 per cent. of the food nitrogen as representing the amount of nitrogen in the feces.

This latter assumption is admittedly a source of error, but this error is probably fairly constant with individual patients and, we believe, does not affect the validity of our conclusions, based as they are on comparative figures.[23]

The analytical methods used were:

Kjeldahl method for total nitrogen; Folin's method for urea, kreatinin, kreatin, total sulphur[24] and its partition among inorganic, ethereal and neutral sulphur, titrated acidity[25] and indican;[26] Boussingault-Shaffer method for ammonia;[27] Folin-Shaffer method for uric acid; Salkowski method for xanthin bases; Volhard method for chlorids; Fehling's or Pavy's methods for sugar; Shaffer's method for beta-oxybutyric acid,[28] and a modified Messinger-Huppert method[28] for acetone plus diacetic acid. The fraction called "rest" nitrogen is the difference between the total nitrogen of the urine and the sum of urea-, ammonia-, kreatinin-, kreatin- and uric-acid nitrogen.

DETAIL OF EXPERIMENTS

PATIENT 1.—R—n, male, aged 23, tailor, fairly well nourished, admitted the seventh day of the disease. Positive serum reaction. Illness severe. Duration of the fever thirty-five days. Two recrudescences.

---

23. The feces of Hoesslin's typhoid subjects (Virchow's Arch. f. path. Anat., 1882, lxxxix, 317) contained on the average about 1 gm. nitrogen per day. Leyden and Klemperer's subjects excreted usually between 1 and 2 gm. nitrogen in the feces, the amount increasing with the nitrogen of the food. In one case the last-named worker assumed the feces-nitrogen to be 10 per cent. of the food nitrogen. In our own analyses, the feces-nitrogen amounts to between 10 and 20 per cent. of the food-nitrogen.

24. Folin, O.: J. Biol. Chem., 1906, i, 131.

25. Folin, O.: Am. Jour. Physiol., 1903, ix, 265.

26. Folin, O.: Am. Jour. Physiol., 1905, xiii, 53.

27. Shaffer, P.: Am. Jour. Physiol., 1903, viii, 330.

28. Shaffer, P.: Jour. Biol. Chem., 1908, iv, 211.

TABLE 1.—PATIENT 1, R—N: TEMPERATURE AND FOOD

Day of Disease.	Temp. F. High.	Temp. F. Low.	Food. Milk c.c.	Cream c.c.	Lactose Gm.	Eggs.	Protein.	Fat.	C.H.
			PERIOD I						
12	104.8	103.0	1200	95	460	2	60.0	99	523
13	104.0	102.0	1080	120	610	2	52.5	101	668
14	104.4	101.0	1200	60	515	2	55.0	89	577
15	104.0	101.4	1470	...	450	2	63.0	84	523
16	103.0	101.6	1000	60	365	2	48.6	79	417
17	102.6	100.6	990	120	420	2	49.5	86	473
18	102.6	99.0	1200	150	455	2	57.0	116	520
19	103.6	100.0	1290	150	510	2	60.0	120	579
	Average						55.7	97	535
			PERIOD II						
20	104.4	101.0	1380	150	500	3	70.0	130	574
21	102.0	98.0	1200	180	500	3	64.8	130	565
22	102.8	98.4	1260	150	480	3	65.2	124	547
23	102.6	98.4	1200	270	500	4	74.2	132	565
24	102.6	99.0	1200	300	505	3	67.0	166	574
25	102.0	99.0	960	300	510	2	52.0	149	567
	Average (omitting last day)						68.2	136	565
			PERIOD III						
26	102.4	99.2	240	420	515	1	23.3	143	540
27	103.6	100.6	....	540	520	..	10.8	162	536
28	104.8	99.6	....	600	515	..	12.0	180	533
29	102.8	101.6	....	630	475	..	12.6	189	494
	Average						15.4	162	536
			PERIOD IV						
30	102.2	99.0	2400	...	...	..	79.2	120	120
31	100.6	99.0	2400	...	...	..	79.2	120	120
32	104.6	101.0	2400	...	...	..	79.2	120	120
33	101.0	99.6	2400	...	...	..	79.2	120	120
34	102.0	99.0	2400	...	...	..	79.2	120	120
35	100.2	98.4	2160	...	...	..	71.5	108	108
Convalescence.			Average (omitting last day)				79.2	120	120
			PERIOD V						
1	99.0	98.0	1200	270	357	2	59.4	152	425
2	98.4	97.0	1440	210	500	3	73.3	151	578
3	99.0	97.6	1440	210	500	4	80.5	156	578
4	99.4	97.2	1440	240	505	5	88.3	171	584
5	100.0	99.0	1410	240	510	4	80.0	164	588
6	99.6	98.4	1500	240	510	5	90.3	174	592
7	99.6	99.0	1560	150	485	5	90.5	150	567
8	99.0	98.0	1620	330	395	5	96.0	207	485
	Average (omitting first day)						85.0	167	564

TABLE 2.—PATIENT 1, R—N: DAILY NITROGEN BALANCE

Day of Disease.	Calories. Total.	Calories. Per Kg.	C. H. Cal. Per Kg.	Nitrogen Balance. Intake.	Nitrogen Balance. Excretion.*	Nitrogen Balance. Balance.
			PERIOD I			
12	3310	61	40	9.6	14.3	—4.7
13	3890	70	51	8.4	10.8	—2.4
14	3430	63	44	8.8	13.8	—5.0
15	3180	59	40	10.1	14.8	—4.7
16	2645	49	32	7.8	15.0	—7.2
17	2940	54	36	7.9	15.7	—7.8
18	3440	64	39	9.1	16.0	—6.9
19	3735	69	44	9.6	11.4	—1.8
			PERIOD II			
20	3850	71	43	11.2	11.9	—0.7
21	3790	70	43	10.4	10.9	—0.5
22	3660	68	41	10.4	9.7	+0.7
23	3850	71	43	11.9	8.9	+3.0
24	4170	77	43	10.7	8.7	+2.0
25	3920	73	43	8.3	8.8	—0.5

TABLE 2.—(CONTINUED)

			PERIOD III			
26	3640	67	41	3.7	7.0	—3.3
27	3750	70	41	1.7	5.1	—3.4
28	3900	72	40	1.9	5.8	—3.9
29	3840	71	38	2.0	....	....
			PERIOD IV			
30	1928	36	9	12.7	11.3	....
31	1928	36	9	12.7	16.6	—3.9
32	1928	36	9	12.7	16.3	—3.6
33	1928	36	9	12.7	15.0	—2.3
34	1928	36	9	12.7	15.5	—2.8
35	1740	..	..	....	....	....
			PERIOD V			
Convalescence.						
1	3390	63	32	9.5	11.0	—1.5
2	4070	75	43	11.7	10.3	+1.4
3	4150	77	43	12.9	9.3	+3.6
4	4340	80	44	14.1	....	....
5	4260	79	44	12.8	10.3	+2.5
6	4420	82	45	14.4	10.3	+4.1
7	4090	76	43	14.5	10.5	+4.0
8	4300	80	37	15.3	12.2	+3.1

• "Excretion"=Total nitrogen of urine + 15 per cent. of food nitrogen.
Weight on twenty-seventh day of disease, 54 Kg.

TABLE 3.—PATIENT 1, R—N: DAILY ANALYSES OF URINE

	Urine					Per Cent. of Total Nitrogen.	
Day of Disease.	Volume c.c.	Gm. Nitrogen. Total.	Kreatinin.	Kreatin.	Rest.•	Urea + NH_3	Rest.•
			PERIOD I				
12	760	12.9	0.54	0.08	1.62	82.8	12.5
13	600	9.5	0.44	0.10	1.52	78.4	16.0
14	800	12.5	0.58	0.09	1.19	85.1	9.5
15	900	13.3	0.60	....	1.70	82.6	12.8
16	960	13.8	0.54	0.21	1.23	84.7	8.9
17	980	14.5	0.54	0.28	1.56	83.6	10.8
18	1580	14.6	0.54	0.42	1.37	84.3	9.4
19	940	10.0	0.53	0.29	0.73	84.7	7.3
			PERIOD II				
20	1180	10.2	0.54	0.25	0.94	83.0	9.2
21	1170	9.3	0.50	0.03	0.84	85.3	9.0
22	1120	8.1	0.44	0.03	0.81	84.3	10.0
23	840	7.1	0.40	0.03	1.01	79.7	14.3
24	810	7.1	0.35	0.00	1.38	75.7	19.4
25	930	7.6	0.47	0.00	1.17	78.5	15.4
			PERIOD III				
26	975	6.4	0.40	0.00	1.10	76.5	17.3
27	1140	4.8	0.42	0.00	0.55	79.5	11.5
28	900	5.5	0.55	0.05	0.95	71.8	17.4
29	Urine lost.						
			PERIOD IV				
30	1450	9.4	0.50	0.00	....	....	....
31	1560	14.7	0.62	....	....	....	....
32	1280	14.4	0.52	0.09	....	....	....
33	1560	13.1	0.47	....	....	....	....
34	970	13.6	0.49	....	....	....	....
35	Urine lost.						
			PERIOD V				
Day of Convalescence.							
1	910	9.6	0.32	....	....	....	....
2	950	8.6	0.39	....	....	....	....
3	780	7.4	0.39	....	....	....	....
4	Urine lost.						
5	1100	8.4	0.49	....	....	....	....
6	1080	8.2	0.45	....	....	....	....
7	940	8.3	0.35	....	....	....	....
8	1160	9.9	0.41	....	....	....	....

• "Rest" includes uric-acid-nitrogen.

TABLE 4.—PATIENT 1, R—N: AVERAGES FROM PERIODS

Figures given for 24 hours.

No. of Days.	Range of Maximum Temp. F. During Period.	Food — Cal. Per Kg. — Total.	Fat.	C. H.	Nitrogen. Gm.	Excretion N.	Balance N.	Urine — Kreatinin N.	Kreatin N.	"Rest" N. — Gm.	Per Cent. Total N.	Kreatinin Coef.
						PERIOD I						
8	104.8-102.6	62	16	41	8.9	13.9	—5.0	0.54	0.21	1.49	11.8	10.0
						PERIOD II*						
5	104.4-102.0	71	23	43	10.9	10.0	+0.9	0.45	0.02	1.02	12.2	8.3
						PERIOD III						
3	104.8-102.4	70	28	41	2.4	5.9	—3.5	0.46	0.02	0.87	15.6	8.5
						PERIOD IV †						
4	104.6-100.6	36	21	9	12.7	15.8	—3.1	0.52	0.09‡	....	....	9.6
						PERIOD V †						
6	Normal	77	29	43	13.6	10.5	+3.1	0.41	....	....	....	7.6

* Last day of period omitted from average.

† First day of period omitted from average.

‡ Result of third day of period.

The experiment began on the twelfth day of the disease and continued thirty-two days, during the last eight of which the temperature was normal.

With the exception of six days, when a strict milk diet was given, the patient received food of high caloric value; and during four days the protein intake was kept very low, maintaining at the same time the high caloric value of the food. The detailed results of this experiment are given in Tables 1, 2 and 3. Throughout the whole experiment there is a fairly close relation between the nitrogen balance and the caloric and protein value of the food.

This experiment may be conveniently divided into five periods, the average results of which are given in Table 4, to which the attention of the reader is particularly directed.

During the first period of eight days (twelfth to nineteenth days of disease) when receiving food equivalent to 62 calories per kg. and 8.9 gm. of nitrogen, the patient *lost an average of 5 gm. of body nitrogen each day.* This is just the type of result which led von Leyden and Klemperer and others to conclude that the harmful effect of the toxins in causing a destruction of body protein cannot be prevented. But, as we shall see, the loss during this period was undoubtedly much less than would have occurred with food of a lower caloric value. In the second period, when the temperature was still fairly high, and the fever process certainly still active, the food was further increased to 71 calories per kg. and 10.9 gm. of nitrogen, with the result that the subject *gained an average of 0.9 gm. nitrogen each day!* Although the nitrogen intake was increased by 2 gm., the excretion was decreased by 3.9 gm. It is clear that during this period the whole of the febrile increase in protein katabolism was either prevented by the large food supply, or was more than compensated for by a retention of food protein.

In interpreting an experiment of this sort we must, of course, remember that the condition of the subject or the intensity of the febrile process is constantly changing, and we must so far as possible make allowance for this factor. The difference between the nitrogen balance of Periods I and II is undoubtedly due in part to such a change in the intensity of the processes involved. On the other hand, we certainly have no reason for believing that the febrile katabolism, including the action of the toxins, had ceased during Period II, and, if this action was still at work, we can scarcely avoid the conclusion that the loss of body protein which would otherwise have taken place was prevented by the high caloric value of the food. In Period I the katabolism was more intense, the demands were greater than the supply, and the subject lost body protein; in

Period II the katabolism was less intense, the food supply was greater than the demand, and the subject gained protein.

In Period IV, the last of fever, pathologic katabolism was still taking place. The food contained more protein (12.7 gm. nitrogen), but equaled only 36 cal. per kg. and the subject lost 3.1 gm. nitrogen per day. In the absence of any increased katabolism, this food should maintain equilibrium. In Period VI, the first six days of normal temperature, the food was again increased to 77 cal. per kg. and the subject gained 3.1 gm. nitrogen per day.

Period III is of interest as showing the importance of at least a moderate amount of protein in the food. The fat and carbohydrate intake was kept practically the same as in Period II, which gave a plus balance of 0.9 gm. nitrogen, but the protein was decreased to a very small amount (average 2.4 gm.) with the result that the patient lost 3.5 gm. nitrogen per day. This loss, however, seems remarkably small under the circumstances; the nitrogen excretion was reduced to 5.9 gm.

It should be noted that the marked sparing of body protein observed during this experiment was accomplished by food very rich in carbohydrate. In four periods the subject received each day carbohydrate equivalent to more than 40 cal. per kg.

The kreatin excretion of this subject is also significant. We shall have frequent occasions to refer to the excretion of kreatin and the following explanation of the bearing of this substance may be stated at this point. Endogenous kreatin is not excreted under normal conditions, but, as has been shown,[29] kreatin is excreted when muscle tissues are being broken down or absorbed. One of the most marked instances of a large excretion of kreatin is in women during the first week postpartum, when, as is known, the involution of the muscular wall of the uterus is proceeding most rapidly. The nitrogen derived from this absorbed protein is excreted at the same time in the urine, resulting in a marked minus balance.[30] This relation is also shown in dogs by the experiments of Murlin.[31]

If, as seems probable to us, the belief is correct that endogenous kreatin is excreted only when protein of muscle tissue is being katabolized, it should be possible to determine from the amount of kreatin excreted approximately the extent of the abnormal destruction or consumption of muscle tissues. While recognizing that this conception has

29. Shaffer: Am. Jour. Physiol., 1908, xxiii, 1.
30. Slemons: Johns Hopkins Hospital Rep., 1905, xii, 121.
31. Murlin: Unpublished work.

not been definitely proved, it appears sufficiently clear to justify its use in the interpretation of our results.

The amount of kreatin excreted in Period I very nearly corresponds with the loss of nitrogen, indicating that the body nitrogen lost was in this period wholly derived from muscles; 0.21 gm. kreatin-nitrogen = 0.65 gm. kreatin. Human muscle contains about 0.4 per cent. kreatin; then 0.65 gm. kreatin = 163 gm. muscle, which ($\times$ 3.4 per cent. nitrogen) equals 5.55 gm. nitrogen. The sudden drop of kreatin on the second day of Period II (Table 3) from 0.25 to 0.03 nitrogen probably indicates a sudden and marked diminution in the pathologic metabolism of muscle protein; whether as a result of the increased food-supply or of a change in the patient's condition it is difficult to decide. Perhaps both are responsible. In the third period, although there was a loss of nitrogen, kreatin was excreted on only one day, indicating that the nitrogen lost was not directly derived from muscle tissues.

During Period IV kreatin unfortunately was determined on only two days, the result on the third day (0.09 gm. nitrogen) being equivalent to about 2.4 gm. muscle-protein-nitrogen. Accepting this day as representative of the period, the kreatin indicates that the greater part of the protein lost was derived from muscle, in which we may suppose the katabolism to have been increased as a result of the decrease in fuel value of the food.

PATIENT 2.—U—h, male, aged 24, laborer, well nourished and of good development, admitted on the tenth day of disease. Blood culture positive. Illness severe. Duration of fever thirty-five days.

The experiment began on the tenth day of the disease and ran for thirty days, during the last eight of which the temperature was normal. This experiment may also be divided into five periods, the average results of which are given in Table 8. The detailed results are given in Tables 5, 6 and 7.

With this subject we see again the marked sparing of the body protein by food rich in carbohydrate, though nitrogen equilibrium was not attained during the fever. In the first period the food contained 9.7 gm. nitrogen and was equivalent to 31 cal. per kg., which fairly represents the diet commonly used in typhoid fever. The patient lost 8.9 gm. of nitrogen each day, and excreted an average of 0.18 gm. kreatin-nitrogen, the latter corresponding to about 4.7 gm. of muscle-protein-nitrogen, and indicating that about half of the nitrogen loss was directly derived from muscle tissue.

In the second period with the temperature fairly high (third week of the disease) the food was increased to 63 cal. per kg., 43 of which were given as carbohydrate. The loss of nitrogen was decreased 5 gm. and the

kreatin almost disappeared, the latter, we think, indicating that the pathologic katabolism of muscle protein was practically stopped.

During the third period the diet was again reduced in fuel value to 31 calories per kg., while the protein intake was somewhat increased. The temperature was lower than in the previous periods, but the loss of nitrogen was very considerably increased. Both kreatin and uric acid were slightly higher than in the second period, indicating an increase in the protein katabolism taking place in the muscles. The amount of kreatin excreted was, however, equivalent to only 1 gm. of muscle-protein-nitrogen, or one-seventh of the amount of the minus balance. The greater part of the nitrogen lost was, therefore, probably derived from the blood or tissue fluids.

The food in the fourth period, the last six days of fever, was again of high caloric value, 66 calories per kg., and the subject was almost in nitrogen equilibrium. The kreatin excreted was about the same as during the preceding period, and just about corresponds to the amount of the minus balance (0.7 gm.) of nitrogen, assuming the latter to have been derived wholly from muscle-protein.

The fifth period consists of seven days of convalescence, during which the food was about the same as during Period IV, except for a slight increase in protein. The subject showed a plus balance of 2.5 gm. nitrogen per day. The small amount of kreatin excreted probably indicates that muscle protein was still being absorbed in very slight degree, though the loss of nitrogen from this muscle protein is more than compensated for by the retention of food nitrogen.

The experiment shows that the addition to the food of carbohydrate equivalent to 32 calories per kg. was followed by a decrease in the nitrogen loss of 5 gm., and the subsequent withdrawal of this carbohydrate resulted in an increase of 3 gm. in the nitrogen loss. On again increasing the carbohydrate intake to 43 carbohydrate calories per kg. the subject lost an average of only 0.7 gm. of nitrogen during the last six days of fever and gained 2.5 gm. (average) during the first seven days of normal temperature.

PATIENT 3.—Z— o, male, aged 20, laborer, well nourished, admitted the fourth day of the disease. Blood culture positive. Illness moderately severe. Sputum blood-stained but no tubercle bacilli could be found, nor any signs of tuberculosis in the lungs.

The experiment began on the ninth day of the disease and continued for thirty-two days, on the last seven of which the temperature was normal. In this experiment, which is divided into six periods, the total nitrogen, kreatinin and kreatin were determined in the urine of each day

as usual, while all of the other determinations were made in "composite" urines representing the whole of the several periods. The latter results are given in Table 12. A summary of results in periods is given in Table 11, and the daily detailed data in Tables 9 and 10.

This is one of the most interesting experiments of the series. During the first period, *at the height of the disease with food equivalent to 32 calories per kg.* and 13.9 gm. nitrogen, the subject *lost only 0.9 gm. nitrogen per day.* The amount of kreatin excreted (0.05 gm. nitrogen) is equivalent to 1.3 gm. muscle-protein-nitrogen. This roughly corresponds to the nitrogen balance and indicates that the nitrogen lost was derived wholly from muscle tissues.

On the other hand, the amount of kreatin excreted as well as the minus balance of nitrogen, was very small. From results of our experiments with other subjects there can be no doubt that with food of lower caloric value this patient would at that time have excreted much kreatin and would have shown a large minus balance of nitrogen during this period. That he did not excrete much kreatin indicates not only a protection afforded to the protein of blood and tissue fluids (circulating protein) from being drawn on as a source of fuel or for other purposes, but a protection of muscle proteins from the mechanism of the "toxic" destruction. Whatever the nature of this protection, it was certainly accomplished by the high caloric value of the food.

In the next period (II) the diet was increased to 85 calories per kg. by the addition of cream, and the subject was practically in nitrogen equilibrium. Only 0.02 gm. of kreatin-nitrogen was excreted, though the temperature was still high, and it seems fair to believe that a pathologic destruction of muscle and other body protein would have taken place but for the large food-supply.

In the third period the diet was kept the same, with the important exception of withdrawing 600 gm. (!) of carbohydrate. The subject received food equivalent to 45 calories per kg., but lost an average of 8.5 gm. nitrogen per day. That the effect of withdrawing carbohydrate is even greater than the above figure indicates is shown by the daily analyses (Table 10). The excretion of nitrogen increased progressively to the last day of the period and might have gone higher. This is probably to be explained by the protection of glycogen stored during the preceding period of high carbohydrate diet. Calculated on the basis of the last two days of the period, the daily loss would be 10.2 gm. of nitrogen.

The kreatin excretion during this period also was small, making it probable that the nitrogen lost was not derived from muscle tissues. Assuming the muscles to be an important seat of the "toxic" destruction,

TABLE 5.—PATIENT 2, U—H: TEMPERATURE AND FOOD

Day of Disease.	Wt. Kg.	—Temp. F.— High.	Low.	Food. Milk c.c.	Cream c.c.	Lactose Gm.	Eggs.	Protein Gm.	Fat Gm.	C. H. Gm.
				PERIOD I						
10	...	104.0	103.0	540	220	180	5	58.0	120	214
11	...	104.0	102.4	600	150	130	3	44.4	91	204
12	...	104.0	102.2	600	225	120	4	50.0	119	157
13	60?	103.5	101.4	2070	...	...	..	68.3	104	104
14	...	103.4	101.6	2160	...	...	..	71.3	108	108
15	...	103.4	101.0	2160	...	...	..	71.3	108	108
Average								60.5	108	149
				PERIOD II						
16	...	103.4	101.0	1200	120	310	6	85.2	128	374
17	...	103.2	100.0	960	120	480	2	48.4	95	332
18	58?	103.0	101.0	1170	45	540	2	54.0	83	600
19	...	103.4	100.0	1200	120	540	2	56.4	107	604
20	...	103.4	100.0	1200	120	540	2	56.4	107	604
Average (excluding 16th day)								53.8	98	585
				PERIOD III						
21	...	103.2	100.8	2160	...	...	..	71.3	108	108
22	...	102.4	99.6	2160	...	...	..	71.3	108	108
23	56?	101.0	99.4	2160	...	...	..	71.3	108	108
24	...	101.0	99.2	2160	...	...	..	71.3	108	108
Average								71.3	108	108
				PERIOD IV						
25	...	102.0	98.0	1140	120	480	2	54.4	104	540
26	...	102.0	99.4	975	120	485	2	49.0	95	537
27	56?	101.0	98.4	990	150	550	2	50.0	105	603
28	...	101.0	98.0	1200	180	550	2	57.6	125	615
29	...	101.0	98.4	1200	240	500	2	58.8	143	567
30	...	100.4	98.4	1200	150	540	2	5.70	116	604
Average (excluding 25th day)								54.5	117	585
				PERIOD V						
Convalescence.										
1	...	99.0	98.0	1170	180	490	2	56.6	123	553
2	...	99.2	98.0	1290	150	515	2.5	63.0	123	584
3	55.0	98.8	98.2	1110	270	500	3	63.6	152	563
4	...	99.2	98.2	1230	300	455	3	68.0	167	525
5	...	99.2	98.2	1200	300	490	3	67.0	166	559
6	55.5	99.0	98.2	1230	240	515	2	59.7	145	584
7	...	98.8	98.4	1140	240	515	3	64.0	145	579
8	...	98.8	98.2	1200	180	500	2	57.8	125	565
Average								63.0	146	566

TABLE 6.—PATIENT 2, U—H: DAILY NITROGEN BALANCE

Day of Disease.	Total Calories.	Food. Cal. Per Kg. Total.	Fat.	C. H.	Nitrogen Gm.	Excretion * N Gm.	Balance N Gm.
			PERIOD I				
10	2230	37	19	15	9.3	20.8	—11.5
11	1860	31	14	14	7.1	....	.....
12	1960	33	19	11	8.0	16.3	— 8.3
13	1670	28	16	7	10.9	20.2	— 9.3
14	1730	29	17	7	11.4	17.9	— 6.5
15	1730	29	17	7	11.4	17.9	— 6.5
			PERIOD II				
16	3070	53	20	26	13.6	19.3	— 5.7
17	2360	56	15	38	7.8	14.2	— 6.4
18	3450	59	13	42	8.6	13.3	— 4.7
19	3710	64	17	43	9.0	11.6	— 2.6
20	3710	64	17	43	9.0	11.2	— 2.2

TABLE 6.—(CONTINUED)

			PERIOD III				
21	1740	31	18	8	11.4	18.0	— 6.6
22	1740	31	18	8	11.4	19.6	— 8.2
23	1740	31	18	8	11.4	18.0	— 6.6
24	1740	31	18	8	11.4	18.0	— 6.6
			PERIOD IV				
25	3410	61	17	40	8.7	14.3	— 5.6
26	3280	59	16	39	7.8	11.2	— 3.4
27	3650	65	17	44	8.0	8.7	— 0.7
28	3920	70	21	45	9.2	9.5	— 0.3
29	3900	70	24	42	9.4	9.5	+ 0.1
30	3780	68	19	44	9.1	8.4	+ 0.7
			PERIOD V				
Day of convalescence.							
1	3640	66	21	41	9.0	....	.....
2	3790	69	21	43	10.1	8.5	+ 1.6
3	3980	72	25	42	10.2	8.8	+ 1.4
4	3980	72	25	39	10.9	8.1	+ 2.8
5	4100	74	25	41	10.7	6.7	+ 3.0
6	3970	72	24	43	9.5	6.9	+ 2.6
7	3980	72	24	43	10.2	6.5	+ 3.7
8	3720	67	21	42	9.3	7.4	+ 1.9

• "Excretion." — Total nitrogen of urine. + 15 per cent. of food nitrogen.

TABLE 7.—PATIENT 2, U—H: DAILY ANALYSES OF URINE

Day of Disease.	Volume c.c.	Urine: Gm. Nitrogen as Total.	NH_3	Kreatinin.	Kreatin.	Uric Acid.	Rest.	Per Cent. of Total Nitrogen. Urea.	NH_3	Rest.
				PERIOD I						
10	920	19.4	1.45	0.74	0.27	0.15	1.29	80.0	7.5	6.6
11	Urine lost.									
12	800	15.1	1.38	0.60	0.07	0.12	1.27	77.4	9.1	8.5
13	1400	18.6	1.77	0.66	0.13	0.14	1.04	79.9	9.5	5.6
14	860	16.2	1.37	0.58	0.17	0.13	0.99	80.1	8.5	6.1
15	880	16.2	1.39	0.64	0.26	0.13	0.93	79.4	8.6	5.7
				PERIOD II						
16	820	17.3	1.51	0.63	0.05	0.13	1.91	75.6	8.8	11.0
17	660	13.0	0.97	0.54	0.04	0.11	1.11	78.7	7.5	8.6
18	760	12.0	1.10	0.56	0.00	0.11	1.00	77.0	9.1	8.3
19	540	10.3	....	0.55	....	....	....	....	...	....
20	670	9.9	0.88	0.54	0.00	0.09	0.64	77.1	8.9	6.5
				PERIOD III						
21	1360	16.3	....	0.56	0.00?	.	1.29	....	...	8.0
22	1390	17.9	0.94	0.53	0.08	0.12	0.90	85.8	5.2	5.0
23	1500	16.3	0.82	0.48	0.02	0.12	0.76	86.5	5.0	4.7
24	1400	16.3	0.79	0.54	0.03	0.12	0.87	85.6	4.9	5.4
				PERIOD IV						
25	1130	13.0	0.63	0.53	0.05	0.10	0.83	83.6	4.9	6.4
26	1020	10.0	0.57	0.50	0.03	0.09	0.83	79.8	5.7	8.3
27	900	7.5	0.50	0.40	0.03	0.07	0.60	78.8	6.7	9.3
28	1240	8.1	0.56	0.47	0.00	0.07	0.50	80.5	6.8	6.1
29	1120	8.1	0.57	0.47	0.05	0.04	0.68	77.6	7.0	8.4
30	1350	7.0	0.52	0.45	0.03	0.05	0.52	77.6	7.4	7.4
				PERIOD V						
Day of Convalescence: 1, urine lost.										
2	1060	7.0	0.45	0.40	....	0.05	0.72	77.1	6.4	10.2
3	1260	7.3	0.46	0.45	....	0.03	0.45	81.0	6.3	6.2
4	1080	6.5	0.38	0.39	0.05	0.03	0.51	79.1	5.8	7.9
5	1040	5.1	0.37	0.31	0.00	0.03	0.63	73.7	7.3	12.4
6	1440	5.5	0.44	0.40	....	0.03	0.77	69.9	8.0	14.1
7	850	5.0	0.38	0.39	0.00	0.04	0.43	75.5	7.5	8.6
8	940	6.0	0.45	0.41	0.01	0.04	0.64	74.3	7.5	10.7

TABLE 8.—PATIENT 2, U—H: AVERAGES FROM PERIODS

No. of Days.	Range of Maximum Temp. F. During Period.	Figures given for 24 hours. Food — Cal. Total.	Per Kg. Fat.	Per Kg. C. H.	Nitrogen Gm.	Excretion N.	Balance N.	Urine — Kreatinin N.	Kreatin N.	Uric Acid N.	"Rest" N. Gm.	"Rest" N. Total N.	Kreatinin Coef.
						PERIOD I							
6	104.0-103.4	31	17	10	9.7	18.6	— 8.9	0.64	0.18	0.13	1.10	6.4	10.6
						PERIOD II*							
5	103.4-103.0	61	16	41	8.6	12.6	— 4.0	0.55	0.01	0.10	0.64	8.1	9.5
						PERIOD III							
4	103.2-101.0	31	18	8	11.4	18.4	— 7.0	0.52	0.04	0.12	0.95	5.7	9.3
						PERIOD IV*							
6	102.0-100.4	66	19	43	8.7	9.4	— 0.7	0.47	0.03	0.07	0.72	8.8	8.4
						PERIOD V*							
7	Normal	71	24	42	10.1	7.6	+ 2.5	0.39	0.01	0.03	0.59	9.7	7.0

* First day of period omitted from average.

TABLE 9.—PATIENT 3, Z—O: TEMPERATURE AND FOOD

Day of Disease.	Wt. Kg.	Temp. High.	Temp. Low.	Food. Milk c.c.	Cream c.c.	Lactose Gm.	Eggs.	Protein Gm.	Fat. Gm.	C. H Gm.
				PERIOD I						
9	....	104.0	102.4	1950	...	590	3	86.0	113	687
10	60.0	103.6	102.0	2000	...	600	3	87.6	116	700
11	....	103.2	101.6	2000	...	600	3	87.6	116	700
12	....	103.2	101.0	2000	...	600	3	87.6	116	700
Average								87.2	115	697
				PERIOD II						
13	60.6	103.6	101.4	2000	300	600	3	93.6	206	709
14	....	103.2	101.2	2000	300	600	3	93.6	206	709
15	....	102.8	101.0	2000	300	600	3	93.6	206	709
16	61.6	103.2	104.4	2000	300	600	3	93.6	206	709
17	61.3	103.6	101.2	2000	300	600	3	93.6	206	709
18	....	103.6	101.0	2000	300	600	3	93.6	206	709
Average								93.6	206	709
				PERIOD III						
19	....	103.6	101.0	2000	300	...	3	93.6	206	109
20	....	103.6	100.6	2000	300	...	3	93.6	206	109
21	60.4	103.8	100.4	2000	300	...	3	93.6	206	109
22	....	103.4	100.2	2000	300	...	3	93.6	206	109
Average								93.6	206	109
				PERIOD IV						
23	....	103.6	99.8	2000	300	670	3	93.6	206	779
24	....	103.4	100.4	2000	300	700	3	93.6	206	809
25	60.0	103.8	99.8	2000	300	750	3	93.6	206	859
26	....	104.8	100.4	2000	300	680	3	93.6	206	789
27	60.0	102.6	100.6	2000	300	690	3	93.6	206	799
28	....	101.8	99.8	1800	270	600	3	86.5	187	695
29	....	101.4	99.2	1800	270	600	3	86.5	187	695
30	....	101.6	99.4	1800	270	600	3	86.5	187	695
Average (excluding first day)								90.6	198	763
				PERIOD V						
31	59.5	100.8	99.2	1800	270	600	3	86.5	187	695
32	....	100.4	98.6	1800	270	660	3	86.5	187	755
33	....	100.4	98.2	1800	270	660	3	86.5	187	755
Convalescence.										
1	....	99.4	98.4	1800	270	660	3	86.5	187	755
2	....	99.8	98.4	1800	270	660	3	86.5	187	755
3	....	99.6	97.8	1800	270	420	3	86.5	187	515
Average								86.5	187	705
				PERIOD VI						
4	....	99.6	98.0	1800	270	...	3	86.5	187	98
5	....	99.6	98.0	1800	270	...	3	86.5	187	98
6	....	99.4	97.8	1800	270	...	3	86.5	187	98
7	....	99.2	97.6	1600	240	...	3	79.2	168	87
Average								84.7	182	95

TABLE 10.—PATIENT 3, Z—O: DAILY NITROGEN BALANCE AND URINE

During Periods III, XIII and XIV, the food contained "somatose."

Day of Disease.	Calories: Total.	Calories: Per Kg.	C. H. Cal. Per Kg.	Nitrogen Balance: Intake Gm.	Nitrogen Balance: Excretion* Gm.	Nitrogen Balance: Balance.	Urine: Volume c.c.	Urine: Nitrogen: Total.	Urine: Nitrogen: Kreatinin.	Urine: Nitrogen: Kreatin.
					PERIOD I					
9	4220	70	47	13.7	15.8	— 2.1	780	13.8	0.67	0.02
10	4330	72	48	14.0	13.1	+ 0.9	640	11.0	0.59	0.03
11	4330	72	48	14.0	15.8	— 1.8	840	13.7	0.59	0.11
12	4330	72	48	14.0	14.5	— 0.5	1140	12.4	0.65	0.05
					PERIOD II					
13	5200	85	48	15.0	15.2	— 0.2	1210	13.0	0.65	0.00
14	5200	85	48	15.0	....	.....	....	....	....	....
15	5200	85	48	15.0	14.7	+ 0.3	1220	12.5	0.52	0.02
16	5200	85	48	15.0	14.0	+ 1.0	1260	11.8	0.55	0.04
17	5200	85	48	15.0	14.9	+ 0.1	1210	12.7	0.53	0.03
18	5200	85	48	15.0	16.6	— 1.6	1660	14.4	0.58	0.02
					PERIOD III					
19	2750	45	7	15.0	21.8	— 6.8	2050	19.6	0.63	0.06
20	2750	45	7	15.0	21.5	— 6.5	1720	19.3	0.56	0.00
21	2750	45	7	15.0	24.4	— 9.4	1520	22.2	0.60	0.03
22	2750	45	7	15.0	25.9	—10.9	1730	23.7	0.61	0.00
					PERIOD IV					
23	5490	91	53	15.0	21.7	— 6.7	1320	19.5	0.63	0.03
24	5620	94	55	15.0	17.3	— 2.3	1040	15.1	0.63	0.02
25	5820	97	59	15.0	15.9	— 0.9	1080	13.7	0.60	0.00
26	5530	92	54	15.0	16.5	— 1.5	1600	14.3	0.60	0.00
27	5580	93	55	15.0	19.9	— 4.9	1260	17.7	0.64	0.00
28	4940	82	47	13.8	17.3	— 3.4	1060	15.1	0.53	0.00
29	4940	82	47	13.8	16.7	— 2.8	900	14.5	0.51	0.05
30	4940	82	47	13.8	17.9	— 4.0	1100	15.7	0.53	0.02
					PERIOD V					
31	4940	83	48	13.8	12.4	+ 1.4	790	10.3	0.43	0.01
32	5180	87	52	13.8	14.2	— 0.4	880	12.1	0.50	....
33	5180	87	52	13.8	13.9	— 0.1	840	11.8	0.52	....
1	5180	87	52	13.8	11.8	+ 2.0	740	9.7	0.45	....
2	5180	87	52	13.8	11.6	+ 2.1	700	9.5	0.47	....
3	4200	71	35	13.8	11.6	+ 2.1	860	9.5	0.45	....
					PERIOD VI					
4	2490	42	7	13.8	13.5	+ 0.3	1340	11.4	0.44	....
5	2490	42	7	13.8	13.0	+ 0.8	1210	10.9	0.45	....
6	2490	42	7	13.8	14.2	— 0.4	1600	12.1	0.46	....
7	2240	38	6	12.7	15.0	— 2.3	2000	12.9	0.54	....

* "Excretion"=Total nitrogen of urine + 15 per cent. of food-nitrogen.

TABLE 11—PATIENT 3, Z—O: AVERAGES FROM PERIODS

Figures are given for 24 hours.

No. of Days.	Range of Maximum Temp. F. During Period.	Food: Cal. Per Kg.: Total.	Food: Cal. Per Kg.: Fat.	Food: Cal. Per Kg.: C. H.	Food: Nitrogen Gm.	Excretion N.	Balance N.	Kreatinin N.	Kreatin N.	Kreatinin Coef.
					PERIOD I					
4	104. -103.2	72	18	48	13.9	14.8	—0.9	0.63	0.05	10.5
					PERIOD II					
6	103.6-102.8	85	32	48	15.0	15.2	—0.2	0.56	0.02	9.2
					PERIOD III					
4	103.8-103.4	45	32	7	15.0	23.5	—8.5	0.60	0.02	10.0
					PERIOD IV *					
8	104.8-101.4	89	31	52	14.5	17.3	—2.8	0.58	0.01	9.6
					PERIOD V					
6	100.8- 99.4	83	29	48	13.8	12.6	+1.2	0.47	....	7.9
					PERIOD VI					
4	Normal	41	28	7	13.5	13.8	(—2.3) —0.3	0.47	....	7.8

* First day of period omitted from average.

TABLE 12.—PATIENT 3, Z—O: DETERMINATIONS MADE IN "COMPOSITE" URINES

Figures given for 24 hours.

Total N. of Urine.	NH_3 N.	Uric Acid N.	Xanthin Bases "Rest." N.	Xanthin Bases Mg. Xanthin.	Per Cent. Total N. Urea.	Per Cent. Total N. NH_3	Per Cent. Total N. "Rest."	Sulphur Gm. Total.	Sulphur Gm. Inorganic.	Sulphur Gm. Ethereal.	Sulphur Gm. Neutral.	Per Cent. of Total S. Inorganic.	Per Cent. of Total S. Ethereal.	Per Cent. of Total S. Neutral	Indican.	Sugar.	Albumin.	Titrated Acidity. N/10 c.c.	Chlorin Gm.	Total N. / 100×Tot. S.
								PERIOD I									Slight			
12.7	1.91	0.24	1.00	23	71.9	15.0	7.9	1.005	0.726	0.040	0.239	72.2	4.0	23.8	0	Trace	+	520	2.6	7.9
								PERIOD II												
13.0	1.25	0.24	0.79	38	78.4	9.6	6.1	0.925	0.710	0.037	0.178	76.8	4.0	19.2	0	0	Trace	543	2.2	7.1
								PERIOD III												
21.0	0.86	0.22	1.09	47	86.9	4.1	5.2	1.408	1.129	0.069	0.210	80.2	4.9	14.9	10	0	Trace	772	2.8	6.7
								PERIOD IV												
15.6	1.09	0.22	1.14	..	79.6	7.0	7.3	1.155	0.919	0.055	0.181	79.5	4.8	15.7	15	Trace	0	610	2.7	7.4
								PERIOD V												
10.4	0.77	0.12	0.70	..	79.8	7.5	6.7	0.746	0.580	0.061	0.105	77.7	8.2	14.1	3	0	0	540	2.7	7.2
								PERIOD VI												
11.5	0.72	0.21	0.62	..	82.2	6.3	5.5	0.810	0.589	0.076	0.145	72.7	9.4	17.9	20	0	0	550	3.6	7.1

it is surprising that in this period, when much body nitrogen was being lost, the muscle protein was not being in part drawn on. It may be that the muscles are protected until the circulating protein has sustained a certain loss, or in this instance the muscles may have been protected during this period of four days by a reserve supply of glycogen accumulated during the previous periods. This explanation is not wholly satisfactory; but the fact remains that those of our subjects who were not given diets of high caloric value excreted, as a rule, much kreatin at the time when they were losing much body protein, while those who received food of high fuel value excreted much less kreatin and, even on withdrawing fat or carbohydrate, these latter patients showed, as a rule, no very considerable amounts of kreatin in the urine. And if our premise is correct, that the appearance of endogenous kreatin in the urine indicates the destruction of muscle protein, the conclusion is warranted that by the diets of large caloric value we in some way protect the muscle tissues from this pathologic katabolism.

In the fourth period much carbohydrate was again added, the food representing 89 calories per kg., 52 of which were in the form of carbohydrate. Excluding the first day of the period, the average balance was minus 2.8 gm. of nitrogen. Why the loss was greater here than in Period II is not clear, but it was much less than in Period III.

During half of Period V the subject had a normal temperature. With food equivalent to 83 calories per kg. there was an average daily gain of 1.2 gm. nitrogen. In Period VI most of the carbohydrate was again withdrawn and the nitrogen excretion rose, giving on the last day a minus balance of 2.3 gm. nitrogen. The temperature was normal and the food contained 13.5 gm. nitrogen and 41 calories per kg. The average balance (— 0.3 gm.) does not fairly represent the period because of the effect, during the first days, of the carbohydrate stored from the preceding period.

PATIENT 4.—W—d, male, aged 23, hotel clerk, well-nourished, taken ill one week before admission. Illness severe. Fever lasted twenty-six days, with mild relapse of seven days' duration. Blood-culture negative. The serum did not react to the typhoid bacillus but was not tried against the intermediates. The whole clinical picture, however, was that of typhoid fever.

The experiment with this patient is to some extent the opposite of the last described (Z—o), and again shows very strikingly the great protection from the loss of body protein afforded by food rich in carbohydrate.

The daily detailed results are given in Tables 13 and 14; Table 15 contains the averages of periods for the nitrogen balance, etc.; and

TABLE 13.—PATIENT 4, W—D: TEMPERATURE AND FOOD

Day of Disease.	Wt. Kg.	Temp. F. High.	Low.	Food. Milk.	Lactose.	Toast.	Butter.	Protein.	Fat.	C. H.
				PERIOD I						
10	....	104.4	102.6	2160	...	...	..	71.3	108	108
11	....	104.4	103.2	2160	...	...	..	71.3	108	108
12	....	103.8	102.6	2400	...	...	..	79.2	120	120
13	63.?	103.6	102.0	2340	...	...	..	77.2	116	116
14	....	103.6	102.0	2400	...	...	..	79.2	120	120
15	....	103.6	102.4	2400	...	...	..	79.2	120	120
16	....	103.4	101.8	2400	...	...	..	79.2	120	120
17	....	103.2	101.8	2400	...	...	..	79.2	120	120
18	....	102.6	101,6	2400	...	...	..	79.2	120	120
Average								78.9	119	119
				PERIOD II						
19	....	102.8	101.0	2400	450	...	..	79.2	120	570
20	....	102.4	101.0	2400	405	...	..	79.2	120	525
21	....	101.0	99.6	2400	450	...	..	79.2	120	570
22	....	102.2	99.8	2400	585	...	..	79.2	120	705
23	....	100.6	99.6	2400	600	...	..	79.2	120	720
24	61.0	100.6	99.0	2310	560	...	..	76.2	116	676
Average								78.7	119	628
				PERIOD III						
Normal Temperature.										
1	....	99.8	98.8	2400	...	...	..	79.2	120	120
2	....	99.4	98.8	2400	...	...	..	79.2	120	120
3	60.2	99.2	98.4	2400	...	...	..	79.2	120	120
4	59.8	98.8	98.0	2400	...	...	..	79.2	120	120
5	....	100.0	98.2	2400	...	...	..	79.2	120	120
Relapse.										
1	....	100.8	99.2	2400	...	90	4	89.0	123	174
Average								79.2	120	120
				PERIOD IV						
2	....	102.4	99.4	2400	505	90	8	89.0	127	679
3	....	102.8	100.6	2400	600	90	48	89.0	161	774
4	61.6	102.8	100.8	2400	600	60	32	85.8	147	756
5	....	101.2	100.0	2400	600	90	24	89.0	140	756
6	61.4	100.2	99.0	2400	600	90	24	89.0	140	756
Convalescence.										
	....	99.8	98.6	2400	600	90	24	89.0	140	756
2	62.3	99.6	98.0	2400	600	90	24	89.0	140	756
3	....	99.6	98.0	2400	600	90	16	89.0	134	756
Average								88.5	143	754
				PERIOD V						
4	62.7	99.2	98.0	2400	...	90	24	89.0	140	174
5	....	99.4	98.0	2400	...	90	24	89.0	140	174
6	....	99.2	98.0	2160	...	90	16	81.2	121	162
7	....	99.6	97.6	2400	...	120	24	93.4	140	192
8	63.0	99.4	97.8	2400	...	120	48	93.4	161	192
9	....	99.4	97.6	2400	...	120	48	93.4	161	192
Average								90.1	145	182

TABLE 14—PATIENT 4, W—D: DAILY NITROGEN BALANCE AND URINE

Day of Disease.	Calories Total.	Calories Per Kg.	C. H. Cal. Per Kg.	Nitrogen Balance Intake.	Nitrogen Balance Excretion.	Nitrogen Balance Balance.	Urine Volume c.c.	Urine Nitrogen as Total.	Urine Nitrogen as Kreatinin.	Urine Nitrogen as Kreatin.
					PERIOD I *					
10	1740	28	07.0	11.4	....	.....	1010	12.4	0.78	....
11	1740	28	07.0	11.4	18.0	— 6.6	1320	16.7	0.67	....
12	1930	31	07.8	12.7	25.2	—12.5	2300	23.9	0.82	....
13	1870	30	07.5	12.3	25.0	—12.7	1570	23.7	0.68	....
14	1930	31	07.8	12.7	24.7	—12.0	2330	23.4	0.70	....
15	1930	31	07.8	12.7	23.9	—11.2	2300	22.6	0.69	....
16	1930	31	07.8	12.7	22.9	—10.2	2550	21.6	0.65	....
17	1930	31	07.8	12.7	23.3	—10.6	2100	22.0	0.62	....
18	1930	31	07.8	12.7	22.6	— 9.9	1660	21.3	0.66	....
					PERIOD II					
19	3770	60	38.0	12.7	....	.....	2060	19.7	0.60	0.05
20	3600	57	35.0	12.7	....	.....	2210	16.4	0.59	0.02
21	3770	60	38.0	12.7	....	.....	1660	14.9	0.63	....
22	4320	70	47.0	12.7	13.6	— 0.9	1320	11.7	0.45	....
23	4390	72	48.0	12.7	13.3	— 0.6	2000	11.4	0.48	....
24	4160	68	45.0	12.2	14.2	— 2.0	1790	12.4	0.49	....
					PERIOD III					
Normal Temperature.										
1	1930	32	08.0	12.7	....	.....	2300	13.9	0.46	....
2	1930	32	08.0	12.7	17.0	— 4.3	2050	15.1	0.45	....
3	1930	32	08.0	12.7	16.7	— 4.0	2080	14.8	0.44	....
4	1930	32	08.0	12.7	16.3	— 3.6	2010	14.4	0.43	....
5	1930	32	08.0	12.7	15.3	— 2.6	2000	13.4	0.45	....
Relapse.										
1	2220	37	12.0	14.2	15.9	— 0.9	1720	13.0	0.54	0.00
					PERIOD IV					
2	4330	72	46.0	14.2	....	.....	1820	11.2	0.61	0.00
3	5040	83	52.0	14.2	11.0	+ 3.2	2000	8.9	0.61	0.00
4	4830	79	50.0	13.7	10.3	+ 3.4	1930	8.1	0.57	0.00
5	4760	78	50.0	14.2	10.8	+ 3.4	1720	8.7	0.56	0.00
6	4760	78	50.0	14.2	10.5	+ 3.7	1730	8.4	0.47	0.03
Convalescence.										
1	4760	77	50.0	14.2	11.1	+ 3.1	1320	9.0	0.47	0.02
2	4760	77	50.0	14.2	10.3	+ 3.9	1730	8.2	0.44	....
3	4710	76	50.0	14.2	9.8	+ 4.4	1420	7.7	0.45	0.00
					PERIOD V					
4	2380	38	11.0	14.2	....	.....	1620	9.2	0.43	0.02
5	2380	38	11.0	14.2	11.9	+ 2.3	1770	9.8	0.41	0.00
6	2130	34	11.0	13.0	12.0	+ 1.0	1600	9.9	0.45	0.01
7	2470	39	13.0	14.9	12.8	+ 2.1	2300	10.6	0.45	0.02
8	2670	43	13.0	14.9	12.5	+ 2.4	2000	10.3	0.46	0.00
9	2670	43	13.0	14.9	13.5	+ 1.4	2180	11.3	0.43	0.05

* Feces in Period I contained 1.26 gm. nitrogen per day.

"Excretion in Period I=total nitrogen of urine + 1.26 gm.

"Excretion in other periods=total nitrogen of urine + 15 per cent. of food nitrogen.

Table 16 the results of sulphur and nitrogen partitions in composite urines representing the several periods.

During the first nine days of the experiment, which began on the tenth day of the disease and continued for thirty-five days, the patient received a strict milk diet, so frequently used in typhoid fever. The food was equivalent to 31 calories per kg. and contained 12.6 gm. of nitrogen. Excluding the first two days of this period, which clearly show the effect of food of high fuel value given during several days before the beginning of the experiment, the average loss per day was 11.3 gm. of nitrogen. Kreatin unfortunately was not determined during this period. During the following six days the food remained the same, except for the addition of much carbohydrate in the form of lactose, the average

TABLE 15.—PATIENT 4. W—D: AVERAGES FROM PERIODS

No. of Days.	Range of Maximum Temp. F. During Period.	Food—Cal. Per Kg.—Total.	Fat.	C. H.	Nitrogen Gm.	Excretion N.	Balance N.	Kreatinin N.
				PERIOD I				
9	104.4-102.6	31	18	8	12.6	23.9*	—11.3	0.69
				PERIOD II				
6	102.8-100.6	65	18	42	12.6	13.7†	— 1.1	0.54
				PERIOD III				
6	99.8-100.8	32	18	8	12.7	16.3‡	— 3.6	0.44
				PERIOD IV				
8	102.4- 99.6	77	21	50	14.2	10.5§	+ 3.7	0.51
				PERIOD V				
6	Normal	40	22	12	14.4	12.6	+ 1.8	0.44

* First two days of period excluded from average.
† First three days of period excluded from average.
‡ First and last days of period excluded from average.
§ First day of period excluded from average.

fuel value of the diet then being 65 calories per kg. There resulted a rapid decline of the nitrogen excretion so that, on the last three of the six days of the period, the subject lost only 1.1 gm. nitrogen each day. This result is perhaps due in part to the simultaneous fall in temperature; but that the added carbohydrate was very largely responsible is shown by the next period (III), when the patient had a normal temperature except on one day. The lactose was withdrawn and there was at once an increase in the nitrogen excretion, giving an average minus balance of 3.6 gm.[32]

32. The first and last days of this period are excluded from the average; the first because of the effect of glycogen stored in the preceding period, the last because of the increase in protein intake.

TABLE 16.—PATIENT 4, W—D: DETERMINATIONS MADE IN "COMPOSITE" URINES—AVERAGES FOR 24 HOURS

Total. N.	NH_3 N.	Uric Acid. N.	Xanthin Bases "Rest." N.	Xanthin Bases Mg. Xanthin.	Per Cent. Total N. Urea.	Per Cent. Total N. NH_3	Per Cent. Total N. "Rest."	Sulphur Gm. Total.	Sulphur Gm. Inorganic.	Sulphur Gm. Ethereal.	Sulphur Gm. Neutral.	Per Cent. of Total S. Inorganic.	Per Cent. of Total S. Ethereal.	Per Cent. of Total S. Neutral.	Chlorin. Gm.	Titrated Acidity. c.c. N/10	Indican.	Sugar.	Albumin.	100×Tot. S. / Total N.
										PERIOD I										
21.0	0.93	0.29	1.10	91	85.6	4.4	5.2	1.570	1.090	0.090	0.390	69.5	5.7	24.8	1.9	420	10	0	Trace	7.5
										PERIOD II										
14.4	0.65	0.23	1.13	37	82.7	4.4	7.5	1.000	0.731	0.034	0.235	73.1	3.4	23.5	1.5	250	20	0	0	7.0
										PERIOD III										
14.2	0.36	0.19	0.56	53	89.0	2.5	4.0	0.901	0.704	0.032	0.165	78.2	3.5	18.3	1.8	210	8	0	0	6.35
										PERIOD IV										
8.7	0.40	0.17	0.77	30	78.5	4.7	8.8	0.638	0.461	0.048	0.129	72.3	7.5	20.2	2.3	240	10	0	0	7.35
										PERIOD V										
10.3	0.32	0.18	0.60	87	85.3	3.1	5.8	0.672	0.521	0.005?	0.146	77.4	0.8?	21.8	3.3	184	20	0	0	6.5

Except for the one day on which the temperature rose to 100.8 F. and which is excluded from the average, this was clinically a period (III) of convalescence; and yet with food equivalent to 32 calories per kg. and to 12.7 gm. of nitrogen the subject lost 3.6 gm. of body nitrogen per day. The conclusion seems warranted that the food was not of sufficient fuel value to prevent or compensate for the excessive protein destruction which was still taking place. It is obvious that the excessive protein katabolism of this period was not due to pyrexia since the temperature was normal.

The following period (IV) includes five days of a relapse and three days of normal temperature. Food of high fuel value, 77 calories per kg., was given throughout and the subject gained nitrogen on each day of the period, the average balance being plus 3.7 gm. Practically no kreatin was excreted. The interpretation seems wholly justified that the large food-supply, consisting chiefly of carbohydrates, completely prevented in this instance the excess of protein katabolism which undoubtedly would otherwise have taken place.

During Period III the temperature was normal, but the subject lost 3.6 gm. nitrogen each day on a diet containing 32 total calories and 8 carbohydrate calories per kg.; during Period IV, in spite of relapse during five of the eight days, he gained 3.7 gm. nitrogen each day on a diet containing 77 total calories and 50 carbohydrate calories per kg. As compared with Period III there was a sparing during Period IV of at least 7.3 gm. $(3.7 - [-3.6] = 7.3)$ of nitrogen per day, which gain is presumably wholly referable to the difference in diet.

Food.	Period III gm.	Period IV gm.
Total cal. per kg	32.0	77.0
Total cal. per kg	32.0	77.0
Carbohydrate cal. per kg	8.0	50.0
Fat—cal. per kg	18.0	21.0

The only marked difference in the diets is in the carbohydrate calories. It appears fair to interpret these figures as showing that the addition of 42 carbohydrate calories per kg. has in this patient spared 7.3 gm. nitrogen or 45.5 gm. of body protein.

In the last period, with normal temperature, the subject showed an average plus balance of 1.8 gm. of nitrogen on a diet equivalent to 40 calories per kg. The increased katabolism had probably ceased and the food was, under the conditions, more than sufficient to maintain equilibrium. The situation here is in sharp contrast with that in Period III when, with normal temperature and food equivalent to 32 calories per

kg., a minus balance of 3.6 gm. was observed; in the latter period the pathologic increase in katabolism was doubtless still taking place.

The comparison of the results in these two periods of normal temperature again illustrates the importance of the intensity of the katabolic process in determining the degree of sparing of body protein accomplished by any given food. This factor explains the difficulty in comparing, quantitatively, a result from one subject with that of another, or even the results from two different periods on the same subject.

PATIENT 5.—B—t, male, aged 23, driver, well-nourished, admitted to hospital on seventh day of disease. Positive blood-culture. Illness moderately severe.

This experiment was intended primarily to determine the relative value of fat versus carbohydrate in protecting the body protein in fever, but it was not carried out as planned and the conclusion on this point is not clear. The experiment does again show the marked effect of carbohydrate, and is of interest also for other reasons.

The experiment began on the ninth day of the disease and continued for thirty-four days, including fifteen days of the original fever and a relapse of eight days. The averages representing the five periods into which the experiment is divided are given in Table 19. Other data are given in Tables 17, 18 and 20.

During the first period of eight days at the height of the disease, the fuel value of the food averaged 56 calories per kg., of which 36 were in fat and 16 in carbohydrates. The subject lost 5.5 gm. nitrogen per day. In the next period (II) the fat was in part withdrawn and more carbohydrate added, so that the average daily food equaled 69 calories per kg., of which 39 were in carbohydrate and 24 in fat. The loss of nitrogen was decreased by 2 gm. The situation is, however, complicated by the lower temperature and the higher total caloric and protein value of the food in the second period; and no conclusion seems to be justified regarding the relative value of fat versus carbohydrate in retarding the loss of nitrogen. There was, however, a marked sparing effect in both of these periods, as shown by Period III, when the temperature was lower than before. The food contained practically the same amount of nitrogen (16.1 gm.) as in Period II, but was equivalent to only 39 calories per kg.; excluding the first day, the average loss was 7.8 gm. nitrogen. On two days of this period the temperature remained below 100 F., while on two other days the highest temperature was only 100.2 and 100.4 F., respectively. On the last day of the period a relapse set in and the temperature reached 101.6. Except on this last day, the patient might be considered clinically almost in the condition of convalescence, but with food, which under normal circumstances would have main-

TABLE 17.—PATIENT 5, B—T: DAILY TEMPERATURE AND FOOD

Day of Disease.	Wt. Kg.	Temp. F. High.	Temp. F. Low.	Milk. c.c.	Cream. c.c.	Eggs.	Lactose Gm.	Toast Gm.	Butter Gm.	Somatose Gm.	Protein Gm.	Fat Gm.	C. H. Gm.
						PERIOD I							
9	....	103.2	101.0	2070	90	1	110	...	24	..	77.4	138	216
10	....	103.8	102.2	1290	480	2	140	60	82	..	73.0	289	255
11	....	103.6	102.4	1320	480	2	140	60	96	..	74.0	292	240
12	75.?	103.2	100.6	1260	420	1	170	90	69	..	67.0	253	300
13	....	?	.....	1290	570	1	170	90	69	..	71.0	299	305
14	....	101.8	100.0	1290	600	1	170	90	69	..	71.0	308	306
15	....	101.8	99.0	1440	540	3	170	90	69	..	90.0	309	312
16	....	101.6	99.2	1320	810	3	160	90	100	..	91.0	410	294
Average											76.8	287	279
						PERIOD II							
17	....	100.6	98.4	2000	...	3	540	90	100	..	97.5	201	694
18	74.?	100.4	98.8	2000	...	3	500	90	84	..	97.5	187	654
19	....	100.2	98.8	2100	...	3	560	120	75	..	104.0	185	737
20	....	100.0	99.8	2100	...	3	560	120	79	..	104.0	188	737
21	....	100.0	98.4	2040	...	3	560	120	79	..	102.0	185	734
22	73.0	100.4	98.6	2000	...	3	495	120	111	..	101.0	210	667
Average											101.0	193	704
						PERIOD III							
23	....	100.2	98.6	2000	...	3	...	120	64	..	101.0	170	172
24	....	99.4	98.4	2000	...	3	...	120	80	..	101.0	184	172
25	72.9	99.8	98.0	2000	...	3	...	120	80	..	101.0	184	172
Relapse.													
1	72.7	100.4	98.4	2000	...	3	...	120	80	..	101.0	184	172
2	....	101.6	99.2	2000	...	3	...	120	80	..	101.0	184	172
Average											101.0	184	172
						PERIOD IV							
3	....	?	.....	2000	...	3	...	120	80	60	147.0	184	172
4	73.0	102.2	100.8	2000	...	3	...	120	80	60	147.0	184	172
5	....	101.8	99.8	2000	...	3	...	120	80	50	131.0	184	172
Average											142.0	184	172
						PERIOD V							
6	73.2	?	99.6	2000	...	3	600	120	80	..	101.0	184	772
7	....	100.8	99.4	2000	60	3	600	120	80	..	102.0	202	775
8	....	100.4	99.0	2000	...	3	600	120	80	..	101.0	184	772
Convalescence.													
1	73.1	99.8	98.0	1800	...	4	540	120	80	..	101.0	179	700
2	....	99.6	98.4	2000	...	4	600	120	80	..	108.0	189	772
3	73.9	99.6	98.0	2000	...	4	600	120	80	..	108.0	189	772
4	....	98.8	98.0	2000	...	4	600	120	80	..	108.0	189	772
5	....	99.8	98.0	2000	...	4	600	120	80	..	108.0	189	772
6	....	99.6	98.2	2000	...	4	600	120	80	..	108.0	189	772
7	74.8	99.8	98.0	2000	...	4	600	120	80	..	108.0	189	772
8	....	99.4	98.0	2000	...	4	600	120	80	..	108.0	189	772
9	....	99.6	98.0	2000	...	4	600	120	80	..	108.0	189	772
Average											107.0	188	765

TABLE 18.—PATIENT 5, B—T: DAILY NITROGEN BALANCE AND URINE

Day of Disease.	Calories—Total.	Calories—Per Kg.	C. H. Cal. Per Kg.	Nitrogen Balance—Intake.	Nitrogen Balance—Excretion.*	Nitrogen Balance—Balance.	Urine—Volume c.c.	Urine—Nitrogen as—Total.	Urine—Nitrogen as—Kreatinin.	Urine—Nitrogen as—Kreatin.
					PERIOD I					
9	2480	33	12.0	12.4	18.4	—6.0	655	16.5	0.80	....
10	4040	54	14.0	11.7	15.6	—3.9	630	13.9	0.68	....
11	4030	54	13.0	11.8	17.4	—5.6	920	15.6	0.77	....
12	3860	51	16.0	10.7	19.2	—8.5	1420	17.6	0.88	....
13	4320	58	17.0	11.3	17.0	—5.7	1080	15.3	0.81	....
14	4400	59	17.0	11.3	18.0	—6.7	880	16.3	0.82	....
15	4530	61	17.0	14.4	18.0	—3.6	950	15.8	0.74	....
16	5400	72	16.0	14.5	19.3	—4.8	1150	17.1	0.67	....
					PERIOD II					
17	5120	69	38.0	15.6	19.1	—3.5	1220	16.8	0.67	0.08
18	4820	65	36.0	15.6	18.3	—2.7	1310	16.0	0.63	0.08
19	5170	70	41.0	16.6	20.6	—4.0	1620	18.1	0.65	....
20	5200	70	41.0	16.6	20.4	—3.8	1520	17.9	0.61	....
21	5150	70	41.0	16.3	20.3	—4.0	1680	17.9	0.61	....
22	5100	70	38.0	16.1	19.7	—3.6	1580	17.3	0.62	....
					PERIOD III					
23	2740	38	9.6	16.1	....	.....	1570	17.5	0.59	....
24	2870	39	9.6	16.1	23.6	—7.5	1850	21.2	0.63	....
25	2870	39	9.6	16.1	23.8	—7.7	1700	21.4	0.63	....
Relapse.										
1	2870	39	9.6	16.1	24.6	—8.5	1900	22.2	0.65	....
2	2870	39	9.6	16.1	23.7	—7.6	1540	21.3	0.65	....
					PERIOD IV					
3	3020	41	9.6	23.5	27.2	—3.7	1850	23.7	0.89	....
4	3020	41	9.6	23.5	27.5	—4.0	2920	24.0	0.84	....
5	2950	40	9.6	21.0	28.9	—7.9	1820	25.4	0.80	....
					PERIOD V					
6	5290	72	43.0	16.1	....	.....	1500	19.5	0.72	....
7	5470	75	43.0	16.3	....	.....	1780	20.5	0.72	0.04
8	5290	72	43.0	16.1	17.4	—1.3	1550	15.0	0.61	0.07
Convalescence.										
1	4950	68	39.0	16.1	16.6	—0.5	1500	14.2	0.62	0.01
2	5370	73	43.0	17.3	17.7	—0.4	1320	15.1	0.59	0.05
3	5370	73	43.0	17.3	17.8	—0.5	1140	15.2	0.60	0.00
4	5370	73	43.0	17.3	17.6	—0.3	1460	15.0	0.62	0.00
5	5370	72	43.0	17.3	17.5	—0.2	1530	14.9	0.63	0.00
6	5370	72	43.0	17.3	17.4	—0.1	1430	14.8	0.67	....
7	5370	72	43.0	17.3	17.2	+0.1	1230	14.6	0.62	0.02
8	5370	72	43.0	17.3	17.4	—0.1	1540	14.8	0.57	0.07
9	5370	72	43.0	17.3	17.1	+0.2	1520	14.5	0.62	0.00

* "Excretion"=total nitrogen of urine + 15 per cent. of food-nitrogen.

TABLE 19.—PATIENT 5, B—T: AVERAGES FROM PERIODS

No. of Days.	Range of Maximum Temp. F. During Period.	Food—Cal. Per Kg.—Total.	Food—Cal. Per Kg.—Fat.	Food—Cal. Per Kg.—C. H.	Nitrogen Gm.	Excretion N.	Balance N.	Kreatinin N.	Kreatin N.
					PERIOD I				
8	103.8-101.6	56	36	16	12.3	17.8	—5.5	0.77	....
					PERIOD II				
6	100.6-100.0	69	24	39	16.2	19.7	—3.5	0.63	0.08
					PERIOD III				
5	101.6- 99.4	39	23	9	16.1	23.9*	—7.8	0.64	....
					PERIOD IV				
3	102.2-101.8	40	23	9	22.7	28.9†	—6.2	0.84	....
					PERIOD V				
12	100.8- 99.4	72	24	43	17.1	17.3‡	—0.2	0.63	0.02

* First day of period excluded from average.
† Excretion of last day taken as representing period.
‡ First two days of period excluded from average.

TABLE 20.—PATIENT 5, B—T: DETERMINATIONS MADE IN "COMPOSITE URINES

Figures given are for 24 hours.

Total N.	NH_3 N.	Uric Acid. N.	"Rest." N.	Xanthin Bases Mg. Xanthin.	Per Cent. Total N. Urea.	NH_3	"Rest."	Sulphur Gm. Total.	Inorganic.	Ethereal.	Neutral.	Per Cent. of Total S. Inorganic.	Ethereal.	Neutral.	Chlorin. Gm.	Titrated Acidity. c.c. $\frac{N}{10}$	Indican.	Sugar.	Albumin.	$\frac{100 \times \text{Tot. S.}}{\text{Total N.}}$
										Period I										
16.0	1.49	0.21	0.52	27	80.7	9.3	3.2	1.140	0.845	0.015	0.280	74.1	1.3	24.6	2.3	530	30	0	Trace	7.1
										Period II										
17.0	0.90	0.21	0.70	44	85.1	5.3	4.1	1.192	0.941	0.047	0.204	79.0	3.9	17.1	4.1	660	80	0	0	7.0
										Period III										
20.5	1.35	0.23	1.60	73	81.3	6.6	7.8	1.353	.....	.....	0.190	....	...	14.0	...	...	..	0	0	6.6
										Period IV										
24.3	0.77	0.27	2.30	81	82.8	3.2	9.5	1.660	1.405	0.040	0.215	84.7	2.4	12.9	4.3	615	6	0	0	6.8
										Period V										
15.5	0.89	0.22	0.60	73	84.6	5.7	3.9	1.150	0.928	0.032	0.190	80.7	2.8	16.5	4.5	640	20	0	0	7.4

tained equilibrium, he lost more than twice as much body nitrogen as in the previous period (II). Even assuming the intensity of the katabolic processes to have been no greater in Period II than in III—and it probably was greater—the additional carbohydrate of Period II (equivalent to about 30 cal. per kg.) appears to have accomplished a sparing of 4.3 gm. nitrogen per day.

During the next three days (Period IV), in the midst of a relapse, the protein intake was increased by the addition of "somatose" to between 21 and 23.5 gm. nitrogen, the total fuel value of the diet remaining at about 40 calories per kg. On account of the lag in excretion, the first two days of the period are excluded and the last day is taken to represent the period. On this day the loss of nitrogen was 7.9 gm., indicating no advantage from the increase of protein intake, though this conclusion is rendered somewhat uncertain by the relapse and the consequent probable further increase in the katabolism of body protein.

During at least the last nine of the twelve days of Period V the subject was in what would ordinarily be called a convalescent condition. His temperature was normal, and clinically his disease was at an end. But, in spite of diet of high caloric value (72 calories per kg.) and containing 17.1 gm. of nitrogen, there was a small loss of body nitrogen throughout the period. A loss of 0.2 gm. of nitrogen per day, of course, is not great and, if less than the estimated 15 per cent. of the food nitrogen was excreted in the feces, there may even have been an actual slight gain of nitrogen. But this difference is of little consequence; the significant thing is that the subject was not gaining three or four grams of nitrogen each day which, according to other experiments, he should have done on such a diet unless a pathologic increase in metabolism was persisting after the fall of temperature. We are inclined to interpret the result in this way: that in this period, as in Period III, the pathologic increase in katabolism continued after the temperature became normal and after the disease was apparently at an end, and that a considerable loss of body nitrogen was prevented by the large food-supply.

PATIENT 6.—L—d, male, aged 32, waiter, fairly well nourished. Moderately severe illness, with a relapse of thirteen days. Positive serum reaction with typhoid bacilli.

The experiment began on the seventeenth day of the disease, almost at the end of fever, and continued for forty-three days, including a relapse of thirteen days' duration. The detailed results are given in Tables 21, 22 and 23, and the averages of periods in Table 24.

During the first period of four days, representing the end of the fever, the patient received food equivalent to 24 calories per kg. and

TABLE 21.—PATIENT 6, L—D: DAILY TEMPERATURE AND FOOD

Day of Disease.	Wt. Kg.	Temp. F. High.	Low.	Food: Milk.	Cream.	Eggs.	Lactose.	Toast.	Protein.	Fat.	C. H.
				PERIOD I							
17	64.5	102.2	99.0	1770	...	..	...	..	58.5	88.5	88.5
18	....	101.4	99.4	1920	...	..	...	..	63.4	96.0	96.0
19	64.0	100.0	99.8	1920	...	..	...	..	63.4	96.0	96.0
20	....	99.4	98.2	1920	...	..	...	..	63.4	96.0	96.0
Average									62.2	94.0	94.0
Normal Temperature.				PERIOD II							
1	....	98.8	97.6	1660	90	..	90	..	57.3	111.0	176.0
2	63.0	99.4	97.8	1680	180	..	210	..	59.0	138.0	300.0
3	....	99.0	98.0	2000	230	..	285	..	70.6	169.0	392.0
4	....	98.6	98.2	1680	120	..	300	..	58.0	120.0	387.0
5	....	98.6	98.2	2000	285	..	285	..	71.7	185.0	393.0
6	62.3	99.2	98.2	1700	180	1	300	..	66.8	144.0	390.0
Average (excluding first day)									65.2	151.0	372.0
				PERIOD III							
7	....	99.6	97.8	1460	180	3	270	..	73.4	143.0	348.0
8	....	99.6	98.4	1210	165	3	225	..	65.0	126.0	290.0
Relapse.											
1	63.5	101.6	98.2	1910	285	3½	360	60	100.5	200.0	499.0
2	....	103.0	99.6	1680	225	3	315	60	88.0	167.0	442.0
3	64.0	103.2	100.6	1890	315	..	360	..	68.6	188.0	464.0
4	63.2	102.8	101.2	1950	180	2	360	..	82.3	162.0	464.0
Average (excluding first day)									80.9	169.0	432.0
				PERIOD IV							
5	....	103.4	100.4	1910	270	1	345	..	75.6	152.0	448.0
6	63.7	103.4	101.2	1760	295	..	295	..	64.0	176.0	393.0
7	....	104.2	101.6	1710	405	2	210	..	78.6	220.0	308.0
8	64.0	103.4	101.4	1160	600	2	105	..	64.7	248.0	180.0
9	....	102.0	100.4	830	630	2	225	..	54.4	240.0	285.0
Average									67.5	207.0	323.0
				PERIOD V							
10	64.0	101.6	100.0	960	600	6	365	..	87.0	260.0	430.0
11	....	101.5	99.6	1080	360	6	570	..	86.0	194.0	635.0
12	....	100.0	99.4	1080	360	6	690	..	86.0	194.0	755.0
13	....	99.8	98.8	1080	360	5.5	690	..	83.0	191.0	755.0
Convalescence.											
2	....	99.4	99.0	1080	360	6	690	..	86.0	194.0	755.0
3	....	99.4	98.6	1080	360	6	540	..	86.0	194.0	605.0
4	....	99.2	98.6	1080	360	6	690	..	86.0	194.0	755.0
	....	99.4	98.8	1120	300	6	690	..	86.0	178.0	755.0
Average (excluding last day. Urine lost)									86.0	203.0	670.0
				PERIOD VI							
5	64.5?	99.6	98.6	1080	360	6	...	..	86.0	194.0	65.0
6	....	99.8	98.4	1080	360	6	...	..	86.0	194.0	65.0
7	....	99.6	98.4	1190	250	6	...	..	87.0	166.0	67.0
8	65.1	99.8	98.0	1080	360	6	...	..	86.0	194.0	65.0
9	....	99.6	98.2	1080	360	6	...	..	86.0	194.0	65.0
Average									86.0	192.0	65.0
				PERIOD VII							
10	....	99.6	98.6	1080	360	6	540	..	86.0	194.0	605.0
11	66.7	99.6	98.2	1080	360	6	690	..	86.0	194.0	755.0
12	....	99.4	98.4	1080	360	6	660	..	86.0	194.0	725.0
13	68.1	99.6	98.6	930	350	6	690	..	81.0	184.0	746.0
14	....	100.0	97.8	1080	360	6	440	..	86.0	194.0	505.0
15	....	99.6	97.6	1080	360	6	360	..	86.0	194.0	425.0
16	....	99.6	98.2	1080	360	6	360	..	86.0	194.0	425.0
17	....	100.0	98.4	1080	360	6	360	..	86.0	194.0	425.0
18	....	100.4	98.2	900	360	6	360	..	80.0	185.0	416.0
19	....	99.2	98.4	1080	360	6	360	..	86.0	194.0	425.0
Average									84.9	192.0	545.0

TABLE 22.—PATIENT 6, L—D: DAILY ANALYSES OF URINE

Day of Disease.	Volume c.c.	Urine Nitrogen as Total	NH_3	Kreatinin.	Kreatin.	U. A.	"Rest."	Per Cent. Total N. Urea	NH_3	"Rest."
					PERIOD I					
17	1590	16.5	0.95	0.47	0.07	0.30	0.80	84.4	5.7	4.8
18	Urine lost.									
19	1520	18.1	1.08	0.47	0.10	0.27	0.60	86.2	6.0	3.3
20	1930	15.8	0.97	0.36	0.16	0.24	0.60	85.3	6.2	3.8
					PERIOD II					
Normal Temperature.										
1	1900	15.5	0.91	0.40	0.14	0.22	0.63	85.2	5.9	4.1
2	1200	11.6	0.76	0.35	0.07	0.18	0.43	84.7	6.6	3.7
3	1380	10.9	0.73	0.34	0.08	0.17	0.68	81.7	6.7	6.3
4	1590	10.2	0.60	0.40	0.00	0.13	0.66	82.5	5.9	6.5
5	1440	8.1	0.56	0.39	0.00	0.12	0.52	80.7	6.8	6.4
6	1480	9.1	0.59	0.42	0.01	0.11	0.40	82.9	6.5	4.4
					PERIOD III					
7	Urine lost.									
8	1040	9.0	0.62	0.44	0.00	0.13	0.56	80.7	6.8	6.2
Relapse.										
1	840	11.4	0.72	0.50	0.00	0.13	0.60	82.7	6.3	5.3
2	2040	10.9	0.82	0.52	0.08	0.12	0.55	80.7	7.5	5.0
3	2340	10.4	0.86	0.49	0.13	0.14	0.55	79.2	8.3	5.3
4	1540	10.5	0.84	0.52	0.02	0.16	0.64	79.2	8.0	6.1
					PERIOD IV					
5	1340	12.9	0.96	0.53	0.00	0.19	0.75	71.1	7.4	5.8
6	1450	12.5	0.92	0.51	0.03	0.19	0.87	80.1	7.3	7.0
7	1940	14.6	1.23	0.56	0.03	0.20	0.94	79.8	8.4	6.5
8	2290	13.7	....	0.48	0.02	....	....	....	...	..
9	1920	11.5	....	0.45	0.01	....	....	....	...	...
					PERIOD V					
10	1640	10.1	....	0.43	0.00	....	....	....	...	...
11	2450	8.2	....	0.43	0.00	....	....	....	...	...
12	1660	7.7	....	0.39	0.00	....	....	....	...	...
13	1900	7.7	....	0.40	0.00	....	....	....	...	...
1	1600	7.6	....	0.40	0.00	....	....	....	...	...
3	1740	7.4	....	0.40	0.04	....	....	....	...	...
3	1580	6.8	....	0.36	0.01	....	....	....	...	...
4	Urine lost.									
					PERIOD VI					
5	2330	9.6	....	0.41	....	....	....	....	...	...
6	1950	10.9	....	0.36	....	....	....	....	...	...
7	2060	13.0	....	0.46	....	....	....	....	...	...
8	1840	11.1	....	0.42	....	....	....	....	...	...
9	1770	10.3	....	0.41	....	....	....	....	...	...
					PERIOD VII					
10	2310	9.7	....	0.43	....	....	....	....	...	...
11	2220	7.3	....	0.41	....	....	....	....	...	...
12	3400	7.2	....	0.45	....	....	....	....	...	...
13	2370	5.4	....	0.50	....	....	....	....	...	...
14	2360	6.5	....	0.50	....	....	....	....	...	...
15	2010	6.9	....	0.41	....	....	....	....	...	...
16	3300	....	....	0.45	....	....	....	....	...	...
17	2630	7.7	....	0.42	....	....	....	....	...	...
18	2010	7.3	....	0.43	....	....	....	....	...	...
19	2750	7.5	...	0.46	....	....	....	....	...	...

TABLE 23.—PATIENT 6, L—D: DAILY NITROGEN BALANCE

Day of Disease.	Food				Excretion N.	Nitrogen Balance.
	Total Calories.	—Cal. Per Kg.— Total.	From C. H.	Nitrogen.		
			Period I			
17	1425	22	6	9.3	17.9	— 8.6
18	1545	24	6	10.1	....	.....
19	1545	24	6	10.1	19.6	— 9.5
20	1545	24	6	10.1	17.3	— 7.2
			Period II			
Normal Temperature.						
1	1985	31	11	9.2	16.9	— 7.7
2	2750	44	20	9.4	13.0	— 3.6
3	3470	55	26	11.3	12.6	— 1.3
4	2940	47	25	9.3	11.6	— 2.3
5	3620	58	26	11.5	9.8	+ 1.7
6	3210	51	26	10.7	10.7	+ 0.0
			Period III			
7	3060	48	23	11.7	....	.....
8	2575	41	19	10.4	10.6	— 0.2
Relapse.						
1	4320	68	32	16.1	13.8	+ 2.3
2	3670	57	29	14.1	13.0	+ 1.1
3	3930	61	30	11.0	12.0	— 1.0
4	3750	59	30	13.2	12.5	+ 0.7
			Period IV			
5	3560	56	29	12.1	14.7	— 2.6
6	3510	55	25	10.2	14.0	— 3.8
7	3620	57	20	12.6	16.5	— 3.9
8	3310	52	12	10.3	15.2	— 4.9
9	3620	57	18	8.7	14.8	— 6.1
			Period V			
10	4540	71	28	13.9	12.2	+ 1.7
11	4750	74	41	13.7	10.3	+ 3.4
12	5250	82	48	13.7	9.8	+ 3.9
13	5230	82	48	13.2	9.7	+ 3.5
Convalescence.						
1	5250	82	48	13.7	9.7	+ 4.0
2	4630	72	39	13.7	9.5	+ 4.2
3	5250	82	48	13.7	8.9	+ 4.8
4	5100	79	48	13.7	....	.....
			Period VI			
5	2420	37	4	13.7	11.1	+ 2.6
6	2420	37	4	13.7	12.4	+ 1.3
7	2170	34	4	13.9	14.5	— 0.6
8	2420	37	4	13.7	12.6	+ 1.1
9	2420	37	4	13.7	11.8	+ 1.9
			Period VII			
10	4630	70	38	13.7	11.7	+ 2.0
11	5250	79	46	13.7	9.3	+ 4.4
12	5120	76	44	13.7	9.2	+ 4.5
13	5100	76	45	13.0	7.3	+ 5.7
14	4220	62	30	13.7	8.5	+ 5.2
15	3900	58	26	13.7	8.9	+ 4.8
16	3900	58	26	13.7	....	.....
17	3900	58	26	13.7	9.7	+ 4.0
18	3760	55	25	12.8	9.2	+ 3.6
19	3900	58	26	13.7	9.3	+ 4.4

TABLE 24.—PATIENT 6, L—D: AVERAGES FROM PERIODS

Figures given are for 24 hours.

No. of Days.	Range of Maximum Temp. F. During Period.	Food: Cal. Per Kg. Total	Food: Fat.	Food: C. H.	Nitrogen. Gm.	Excretion N.	Balance N.	Urine: Kreatinin N.	Urine: Kreatin N.	Urine: NH_3 N. Gm.	Urine: NH_3 N. Per Cent. of Total N.	Urine: "Rest" N. Gm.	Urine: "Rest" N. Per Cent. of Total N.	Uric Acid. N.	Xanthin Bases Mg. Xanthin.	Kreatinin Coef.
							PERIOD I									
4	102.2- 99.4	24	13	6	10.0	18.3	—8.3	0.43	0.11	1.00	6.0	0.67	4.0	0.27	42‡	6.7
							PERIOD II									
6	Normal	51	22	24	10.4	11.5*	—1.1	0.38	0.03	0.65	6.5	0.54	5.4	0.14	48‡	6.0
							PERIOD II									
6	99.6-103.0	58	25	28	12.9	12.3	+0.6	0.51	0.06	0.81	7.8	0.58	5.6	0.14	..	8.0
							PERIOD IV									
5	103.4-102.0	55	30	21	10.8	14.6	—3.8	0.51	0.02	1.04†	7.7	0.85†	6.4	0.20	52‡	8.0
							PERIOD V									
8	101.6- 99.2	78	29	43	13.7	9.9	+3.8	0.40	0.00	....	...	....	...	0.16‡	..	6.2
							PERIOD VI									
5	Normal	37	27	4	13.7	12.5	+1.2	0.41	....	....	...	....	...	0.15‡	..	6.4
							PERIOD VII									
10	Normal	64	26	33	13.6	9.3	+4.3	0.45	....	....	...	....	...	0.13‡	..	6.7

* First day of period excluded from average.

† Average of first three days of period.

‡ Determination made in "composite" urines.

containing 10 gm. of nitrogen. A daily minus balance of 8.3 gm. of nitrogen was found, and 0.11 gm. of kreatin-nitrogen was excreted. Both of these results are of very considerable interest, showing, as they do, that, with a somewhat inadequate food-supply, the protein katabolism was still very markedly increased, when the disease, as indicated by the temperature and clinical condition of the subject, had practically run its course. Attention is particularly called to the considerable excretion of kreatin at this time.

In the second period of six days, during which the temperature was normal, the energy value of the food was doubled (51 cal. per kg.), which was immediately followed by a sharp decline in the excretion of nitrogen and of kreatin as well.

Excluding the first day of the period, in which the effect of the high caloric diet is not seen, the averages for the period are: a minus balance of 1.1 gm. nitrogen (as compared with 8.3 gm. of the preceding period), and 0.03 gm. kreatin-nitrogen.

Four of the six days of Period III were the beginning of a relapse. The patient received food equivalent to 58 cal. per kg. and containing 12.9 gm. of nitrogen. Excluding the first day of the period, the urine of which was lost, there was an average plus balance of 0.6 gm. nitrogen and 0.06 gm. kreatin-nitrogen; the kreatin indicating a somewhat greater absorption of muscle protein, which was more than compensated for by the retention of other protein. The next five days, Period IV, representing the height of the relapse, the patient received food equal to 55 calories per kg. and 10.8 gm. nitrogen, nearly as much as in the preceding period, but this was not sufficient to counterbalance or prevent a marked increase in the protein katabolism, and the subject lost an average of 3.8 gm. nitrogen each day. This loss, however, quickly stopped when the food was increased to 78 calories per kg. and 13.7 gm. nitrogen, the average of the next period (V).

During each of the eight days of this period (V), on three of which the temperature was above normal, the subject showed a plus balance of nitrogen, the average being 3.8 gm. Practically no kreatin was excreted.

For the following five days of normal temperature the greater part of the carbohydrate was withdrawn from the food, which was otherwise the same as in Period V, and represented 13.7 gm. nitrogen and 37 calories per kg. The excessive endogenous katabolism of protein observed in earlier periods had ceased and this diet was more than sufficient for equilibrium, the subject gaining 1.2 gm. nitrogen per day.

In the last period (VII) much carbohydrate was again added and an average plus balance of 4.3 gm. nitrogen was found. Carbohydrate

equivalent to about 30 calories per kg. added to the food caused an increased retention of 3.1 gm. nitrogen (4.3-1.2) per day for ten days.

PATIENT 7.—G—t, male, aged 38, tinsmith, admitted on the twenty-first day of the disease, claimed to have lost 15 pounds, but looked well-nourished. Illness very severe. Duration of fever forty-seven days, followed by a relapse of twenty-seven days. Complicated by serofibrinous pleurisy, cholecystitis with jaundice, and several slight intestinal hemorrhages. Sputum bloody but no tubercle bacilli could be found.

The experiment with this patient is the longest of this series. Our observations began on the thirtieth day of the disease, which was twenty days before the temperature remained normal for the first time, and continued for seventy-two days, on forty-seven of which fever was present. In spite of this long and very severe illness, the patient weighed about 2 kg. more at the end than at the start of the experiment. According to the sum of the daily balances of nitrogen, there was during the experiment a total loss of about 150 gm. (allowing 20 gm. for the days on which the urine was lost) and a total gain of 243 gm., giving a net gain of about 93 gm. of nitrogen. This is the equivalent of about 2.9 kg. of muscle tissue.[33]

The seventy-two days of the experiment are divided into fifteen periods, the average results of which are given in Table 28. The daily data are given in Tables 25, 26 and 27.

During the time of Periods I to IV, and VII to XI, inclusive, the patient had a fever temperature, while in the remaining periods the temperature was practically normal. In Period I there was an average daily loss of 7.7 gm. nitrogen (excluding the first two days, when the protein intake was very low) with food of an average value of 32 cal. per kg. and 9.2 gm. nitrogen. During the next three days (II) the food was increased by the equivalent of 21 cal. per kg. in the form of carbohydrate, and the nitrogen loss was decreased by 5.5 gm. per day. This result is probably in part due to a lowered intensity of the katabolic processes coincident with the fall in temperature, because in the two following periods (III and IV) a slight plus balance was obtained, though the food was of less caloric value (but of higher protein value) than in Period II.

In Periods V and VI the temperature was about normal and the protein katabolism was not markedly abnormal; minus balances of 0.6 and 0.7 gm. nitrogen were obtained with food equivalent to 28 and 27 cal. per kg.

---

33. The loss of nitrogen during the first thirty days of the disease, before the experiment began, was of course great and probably more than offsets the above gain.

TABLE 25.—PATIENT 7. G—T: DAILY FOOD

Day of Disease.	Milk. c.c.	Cream. c.c.	Eggs.	Lactose. Gm.	Butter. Gm.	Toast. Gm.	Beef Extract. Gm.	Somatose. Gm.	Whisky. c.c.	Protein. Gm.	Fat. Gm.	C. H. Gm.
						PERIOD I						
30	640	150	..	270	...	...	..	..	..	24.1	77	306
31	400	100	..	600	...	...	..	..	60	15.2	50	623
32	1500	...	..	330	...	...	..	..	50	49.5	75	405
33	1500	...	..	120	...	...	..	..	90	49.5	75	285
34	2000	...	..	...	...	...	..	..	90	66.0	100	100
35	1800	60	..	185	...	...	..	..	90	60.6	108	277
36	2000	...	..	...	...	...	..	..	90	66.0	100	100
37	2000	...	..	...	...	...	..	..	90	66.0	100	100
38	1230	120	..	345	...	...	..	..	75	43.0	97	410
Average (excluding first two days)										57.2	93	240
						PERIOD II						
39	1350	150	..	520	...	...	..	..	75	47.0	112	592
40	1435	60	..	505	...	...	..	..	90	48.5	90	578
41	1440	60	..	493	...	...	..	..	90	48.7	90	567
Average										48.0	97	579
						PERIOD III						
42	1350	60	..	455	...	...	..	60	90	94.0	85	526
43	1110	60	..	410	...	...	..	60	90	84.5	73	467
44	1110	60	..	290	...	...	..	60	90	84.5	73	347
Average										87.7	77	447
						PERIOD IV						
45	1470	60	1	345	...	...	..	..	90	57.0	97	420
46	1470	60	2	345	...	...	..	..	90	64.2	102	420
47	1410	60	2	305	...	...	..	..	90	62.0	99	377
48	1410	60	2	365	...	...	..	..	90	62.0	99	437
Average (excluding first day of period)										62.7	100	411
						PERIOD V						
49	2190	...	..	...	...	...	..	..	90	72.3	110	110
50	2190	...	..	...	...	...	..	..	90	72.3	110	110
51	2190	...	..	...	...	...	..	..	90	72.3	110	110
Average										72.3	110	110

Day of Disease.	Milk. c.c.	Cream. c.c.	Eggs.	Lactose. Gm.	Butter. Gm.	Toast. Gm.	Beef Extract. Gm.	Somatose. Gm.	Whisky. c.c.	Protein. Gm.	Fat. Gm.	C. H. Gm.
						PERIOD VI						
52	2400	...	..	...	...	...	60	..	..	79.2*	120	120
53	1920	...	..	...	...	...	60	..	..	63.3*	96	96
Average										71.2*	108	108
						PERIOD VII						
54	795	390	4	195	...	...	..	..	..	62.8	178	246
55	1080	330	4	360	...	30	..	..	..	74.4	174	442
56	1320	270	4	320	30	60	..	..	..	84.4	194	427
57	1290	270	5	310	...	...	..	..	..	84.0	172	380
58	1140	270	4	280	...	...	..	..	..	71.8	159	345
Average (excluding first day of period)										78.6	175	398
						PERIOD VIII						
59	1440	300	2	325	...	...	..	..	..	68.0	173	406
60	1380	600	3	190	...	...	..	..	..	72.0	260	277
61	1260	480	2	300	...	...	..	..	..	65.5	218	377
62	1260	480	2	240	...	...	..	..	..	65.5	218	377
Average										67.8	216	344
						PERIOD IX						
63	520	240	1	180	...	...	..	..	..	29.0	103	213
64	480	240	..	...	...	...	51	..	..	20.6	96	171
65	1020	120	..	140	...	...	..	..	..	36.0	87	195
66	1590	90	..	160	...	...	..	..	..	54.3	107	242
67	1820	120	..	160	...	...	..	..	..	62.4	127	255
68	2160	...	..	180	...	...	..	..	..	71.4	108	288
69	2160	...	..	180	...	...	..	..	..	71.4	108	288
70	2160	...	..	180	...	...	..	..	..	71.4	108	288
Average (last three days of period)										71.4	108	288
						PERIOD X						
71	2160	...	1	180	...	...	..	..	..	78.5	113	288
72	2160	...	2	155	...	...	..	..	..	85.7	119	263
73	2160	...	2	150	...	...	..	..	..	85.7	119	258
74	2160	...	2	180	...	...	..	..	..	85.7	119	288
75	2160	...	2	180	...	...	..	..	..	85.7	119	288
76	2160	...	2	315	...	...	..	..	..	85.7	119	421
Average										84.5	118	301

* Does not include nitrogen of beef extract

TABLE 25.—(CONTINUED)

Day of Disease.	Milk. c.c.	Cream. c.c.	Eggs.	Lactose. Gm.	Butter. Gm.	Toast. Gm.	Beef Extract. Gm.	Somatose. Gm.	Whisky. c.c.	Protein. Gm.	Fat. Gm.	C. H. Gm.
						PERIOD XI						
77	2160	180	3	405	8	30	..	..	..	99.8	190	536
78	2040	255	4.5	385	16	...	..	..	..	104.8	225	495
79	1920	240	4	360	16	...	..	..	..	97.0	210	463
80	2160	270	5	540	76	60	..	..	..	119.3	291	692
81	1920	240	4	480	61	60	..	..	..	103.6	249	619
82	2160	180	5	180	106	60	..	..	..	117.5	288	329
83	2160	210	5	540	106	105	..	..	..	123.1	297	717
84	2400	300	5	540	136	90	..	..	..	131.2	362	723
Average										112.0	264	572
						PERIOD XII						
85	2160	270	5	...	136	90	..	..	..	122.6	332	170
86	2400	300	5	...	135	120	..	..	..	134.4	352	201
87	2400	210	5	...	103	120	..	..	..	132.6	298	198
88	2400	300	5	...	111	120	..	..	..	134.4	332	191
89	1680	240	5	330	111	150	..	..	..	112.8	278	511
Average										127.4	318	254
						PERIOD XIII						
90	2400	330	5	520	111	150	..	60	..	183.0	320	740
91	2400	300	5	600	111	150	..	60	..	182.4	311	820
92	2400	300	5	600	111	150	..	60	..	182.4	311	820
93	2160	270	5	600	87	120	..	60	..	172.5	290	788
94	2160	270	5	600	111	150	..	60	..	176.0	310	806
Average										179.0	317	795
						PERIOD XIV						
95	2400	300	5	...	111	150	..	60	..	184.0	331	219
96	2400	300	5	...	111	150	..	60	..	184.0	331	219
97	2400	300	5	...	111	150	..	30	..	161.0	331	219
Average										176.0	331	219
						PERIOD XV						
98	2400	300	5	...	111	150	..	..	..	127.7	331	219
99	2400	300	5	...	111	150	..	..	..	127.7	331	219
100	2400	300	5	...	111	120	..	..	..	124.4	331	201
101	2160	300	5	...	120	165	..	..	..	131.4	327	216
Average										127.8	330	214

TABLE 26.—PATIENT 7, G—T: DAILY ANALYSES OF URINE *

Day of Disease.	Volume c.c.	Nitrogen			
		Total.	Kreatinin.	Kreatin.	Uric Acid.
		PERIOD I			
30	750	16.0	0.50	0.10	0.25
31	950	18.3	0.63	0.15	0.33
32	1570	12.0	0.51	0.01	0.28
33	2450	16.3	0.54	0.13	0.32
34	1970	16.3	0.50	0.19	0.23
35	1050	14.3	0.39	....	....
36	1590	15.5	0.37	0.17	0.24
37	1490	15.3	0.43	0.11	0.23
38	1490	15.3	0.43	0.11	0.23
		PERIOD II			
39	740	8.9	0.36	0.01	0.22
40	1000	9.0	0.50	0.09	....
41	800	8.4	0.45	0.04	....
		PERIOD III (Somatose)			
42	920	9.1	0.39	0.07	....
43	1860	10.5	0.46	0.04	....
44	1620	11.1	0.41	0.07	....
		PERIOD IV			
45	1920	11.0	0.43	0.05	....
46	1670	8.8	0.41	0.00	....
47	1740	8.3	0.41	0.02	....
48	1430	7.9	0.36	0.05	....
		PERIOD V			
49	2060	8.8	0.38	0.02	....
50	2060	10.2	0.39	0.03	....
51	1940	10.8	0.41	0.02	0.11
		PERIOD VI (Meat Extract)			
52	2135	12.3	0.72	0.21	0.30
53	2040	15.0	0.86	0.40	0.49
		PERIOD VII			
54	1580	10.4	0.40	0.01	0.19
55	1320	7.3	0.39	0.00	....
56	1900	7.4	0.43	0.00	....
57	1950	7.7	0.47	0.00	....
58	1880	7.7	0.47	....	....
		PERIOD VIII			
59	1360	5.8	0.36	0.06	....
60	2650	6.9	0.40	0.12	....
61	2040	6.9	0.48	....	....
62	2340	7.8	0.53	....	....
		PERIOD IX			
63	1870	8.4	0.58	....	....
64	2000	14.6	0.84	Meat Extract	....
65	1380	14.9	0.55	....	....
66	Urine lost.				
67	Urine lost.				
68	860	12.7	0.60	....	....
69	Urine lost.				
70	1160	13.7	0.52	....	....
		PERIOD X			
71	1330	12.5	0.50	....	....
72	1300	12.3	0.47	....	....
73	1320	11.8	0.56	....	....
74	1200	11.7	0.56	....	....
75	1400	10.1	0.53	....	....
76	1600	11.0	0.48	....	....

* During Period VI, and on second day of Period IX, subject was given meat extract. During Periods III, XIII and XIV, the food contained "somatose."

TABLE 26.—(CONTINUED)

Day of Disease.	Volume c.c.	Nitrogen—Total.	Kreatinin.	Kreatin.	Uric Acid
		PERIOD XI			
77	1440	9.8	0.49	....	....
78	1660	8.4	0.41	....	....
79	1860	8.8	0.39	....	....
80	1560	8.0	0.39	....	....
81	1660	9.3	0.41	....	....
82	1580	7.3	0.36	....	....
83	1680	8.6	0.42	....	....
84	1830	8.4	0.36	0.02	....
		PERIOD XII			
85	2360	9.3	0.37	0.02	....
86	2140	10.7	0.36	0.02	....
87	2225	11.4	0.34	....	....
88	1860	11.2	0.35	....	....
89	1700	10.1	0.38	....	....
		PERIOD XIII (Somatose)			
90	1860	8.6	0.36	....	....
91	1600	8.3	0.37	....	....
92	2150	8.5	0.35	....	....
93	2700	8.3	0.35	....	....
94	2660	9.6	0.37	....	....
		PERIOD XIV (Somatose)			
95	3040	11.9	0.44	0.00	....
96	2410	14.7	0.41	0.00	....
97	2210	15.3	0.39	0.00	....
		PERIOD XV			
98	2140	14.0	0.35	0.00	....
99	2250	13.9	0.39	0.00	....
100	1620	11.5	0.33	0.03	....
101	2000	13.6	0.38	0.02	....

TABLE 27.—PATIENT 7, G—T: DAILY TEMPERATURE AND NITROGEN BALANCE *

Day of Disease.	Wt. Kg.	Temp. F.—High.	Low.	Total Cal.	Cal. Per Kg.—Total.	C. H.	Nitrogen Balance.—Intake.	Excretion.	Balance.
				PERIOD I					
30	67.0	105.0	103.2	2065	31	19	3.8	16.6	—12.8
31	....	104.0	103.0	3085	46	38	2.4	18.7	—16.3
32	67.4	104.2	102.6	2570	38	25	7.8	13.2	— 5.4
33	....	104.0	103.2	2075	31	17	7.8	17.5	— 9.7
34	....	104.8	102.0	1610	24	6	10.5	17.9	— 7.4
35	65.6	104.0	103.2	2390	36	18	9.7	15.7	— 6.0
36	....	103.6	102.0	1610	24	6	10.5	17.1	— 6.6
37	....	103.4	102.2	1610	24	6	10.5	16.6	— 7.9
38	....	103.0	101.4	2760	42	26	6.9	16.6	— 7.9
				PERIOD II					
39	65.9	103.4	100.4	3660	56	37	7.5	10.0	— 2.5
40	....	103.2	100.4	3405	52	36	7.7	10.1	— 2.4
41	....	102.8	100.0	3350	52	36	7.8	9.6	— 1.8
				PERIOD III					
42	64.5	102.6	100.4	3330	52	33	15.0	(11.3)	(+ 3.7)
43	....	103.2	99.6	2950	46	30	13.5	12.5	+ 1.0
44	63.5	102.8	99.8	2450	38	22	13.5	13.1	+ 0.4
				PERIOD IV					
45	63.3	101.4	99.4	2860	45	27	9.1	(12.4)	(— 3.3)
46	....	102.2	98.8	2920	46	27	10.3	10.3	+ 0.0
47	63.5	101.2	98.8	2720	43	24	9.9	9.8	+ 0.1
48	....	100.6	98.6	2960	47	28	9.9	9.4	+ 0.5

* In Period VIII, the feces contained 1.8 gm. N. per day. In other periods "excretion"=total N. of urine + 15 per cent. of food N.

TABLE 27.—(CONTINUED)

Day of Disease.	Wt. Kg.	—Temp. F.— High.	Low.	Total Cal.	Cal. Per Kg. Total.	C. H.	—Nitrogen Balance.— Intake.	Excretion.	Balance.
				PERIOD V					
49	64.0	100.2	98.4	1765	28	7	11.5	(10.5)	(+ 1.0)
50	....	100.0	97.6	1765	28	7	11.5	11.9	— 0.4
51	62.5	100.4	98.4	1765	28	7	11.5	12.3	— 0.8
				PERIOD VI					
52	....	100.0	98.2	1930	31	8	18.0	(15.0)	(+ 3.0)
53	....	99.8	98.6	1540	24	6	15.4	17.3	— 1.9
				PERIOD VII					
54	....	100.4	98.8	2920	46	16	10.0	11.9	— 1.9
55	....	101.6	99.2	3740	60	29	11.9	9.1	+ 2.8
56	....	102.6	99.6	3900	62	28	13.5	9.6	+ 3.9
57	....	103.8	100.0	3500	55	25	13.4	9.9	+ 3.5
58	....	102.6	99.2	3190	50	22	11.5	9.4	+ 2.1
				PERIOD VIII					
59	....	101.8	98.8	3550	56	26	10.9	7.6	+ 3.3
60	....	101.8	99.4	3850	60	18	11.5	8.7	+ 2.8
61	....	102.6	99.8	3850	60	24	10.5	8.7	+ 1.8
62	....	103.4	100.6	3600	56	20	10.5	9.6	+ 0.9
				PERIOD IX					
63	....	104.4	102.4	1950	30	14	4.6	10.2	— 5.6
64	....	104.8	103.2	1680	26	11	8.1	16.4	— 8.3
65	....	104.6	103.6	1760	27	12	5.8	16.7	—10.9
66	....	104.8	103.4	2210	34	15	8.7	....	.....
67	65.1	104.2	102.8	2480	38	16	10.0	....	.....
68	....	104.8	102.8	2480	38	18	11.4	14.5	— 3.1
69	....	104.8	102.8	2480	38	18	11.4	....	.....
70	64.2	104.2	102.8	2480	38	18	11.4	15.5	— 4.1
				PERIOD X					
71	....	103.6	101.8	2550	40	18	12.5	14.4	— 1.9
72	....	104.0	102.4	2530	39	17	13.7	14.4	— 0.7
73	....	103.2	101.2	2520	39	16	13.7	13.9	— 0.2
74	....	102.6	101.4	2740	43	18	13.7	13.8	— 0.1
75	....	102.6	101.4	2740	43	18	13.7	12.2	+ 1.5
76	....	102.5	100.2	3180	49	26	13.7	13.1	+ 0.6
				PERIOD XI					
77	....	102.4	100.4	4373	68	34	16.0	12.2	+ 3.8
78	....	102.0	99.5	4546	71	31	16.7	10.9	+ 5.8
79	....	101.0	99.0	4253	66	29	15.5	11.1	+ 4.4
80	....	100.8	98.6	6040	94	44	19.1	10.9	+ 8.2
81	....	101.4	98.4	5280	82	39	16.6	11.8	+ 4.8
82	....	100.0	98.6	4510	70	21	18.8	10.1	+ 8.7
83	....	100.4	98.4	6210	96	46	19.7	11.6	+ 8.1
84	....	100.2	98.6	6860	106	46	21.0	11.6	+ 9.4
				PERIOD XII					
85	....	99.8	98.6	4290	67	11	19.6	12.2	+ 7.4
86	....	99.8	98.4	4645	72	13	21.5	13.9	+ 7.6
87	....	99.6	98.4	4126	64	13	21.2	14.6	+ 6.6
88	....	99.6	98.4	4425	69	12	21.5	14.4	+ 7.1
87	64.6	100.2	98.6	5140	80	32	17.9	12.8	+ 5.1
				PERIOD XIII					
90	....	100.4	98.6	6760	104	47	29.3	13.0	+16.3
91	....	99.8	98.8	7000	107	52	29.2	12.7	+16.5
92	65.0	99.6	98.4	7000	107	52	29.2	12.9	+16.3
93	....	100.4	99.8	6640	102	50	27.6	12.4	+15.2
94	....	100.2	99.4	6900	106	51	28.2	13.8	+14.4
				PERIOD XIV					
95	....	100.6	99.0	4730	71	13	29.4	16.3	(+13.1)
96	....	100.4	99.0	4730	71	13	29.4	19.0	(+10.4)
97	68.2	100.2	98.6	4640	68	13	25.8	19.2	(+ 6.6)
				PERIOD XV					
98	68.7	99.8	98.2	4500	65	12	20.4	17.1	+ 3.3
99	....	99.8	98.4	4500	65	12	20.4	17.0	+ 3.4
100	....	99.4	98.4	4410	64	12	19.9	14.5	+ 5.4
101	68.8	100.0	98.4	4460	65	12	21.0	16.7	+ 4.3

TABLE 28.—PATIENT 7, G—T: AVERAGES OF PERIODS

Figures given for 24 hours.

	No. of Days.	Range of Maximum Temp. During Period.	Food: Cal. Per Kg. Total.	Food: From Fat.	Food: From C. H.	Food: Nitrogen. Gm.	Excretion N.[10] Gm.	Nitrogen Balance. Gm.	Urine: Total Nitrogen.	Urine: Kreatinin N.	Urine: Kreatin N.	Urine: NH_3 N. Gm.[1]	Urine: NH_3 N. Per Cent. Total N.	Urine: Uric Acid N.	Urine: "Rest" N. Gm.[1]	Urine: "Rest" N. Per Cent. Total N.	Urine: Urea. Per Cent. Total N.[1]	Urine: Xanthin Bases. Gm. Xanthin.[1]	Kreatinin Coef.
Period I[1]	9	105.0-103.0	32	13	15	9.2	16.9	— 7.7	15.5	0.48	0.12	1.13	7.1	0.25	1.46	9.2	77.9	0.040	7.3
Period II	3	103.4-102.8	54	14	36	7.7	9.9	— 2.2	8.8	0.44	0.04	0.82	9.6	0.24[1]	1.02	11.6	69.9	.....	6.8
Period III	3	103.2-102.6	45	11	29	14.0	12.8[5]	(+ 0.4) + 1.2	10.8	0.42	0.06	....	....	0.26[1]	1.00	9.8	....	0.086	6.5
Period IV[4]	4	102.2-100.6	45	15	27	10.0	9.8	+ 0.2	8.3	0.39	0.02	0.59	7.2	0.20[1]	0.88	10.7	74.5	0.063	6.1
Period V	3	100.4-100.0	28	16	7	11.5	12.2[5]	— 0.7	10.5	0.40	0.02	....	....	0.11	....	....	....	.....	6.3
Period VI[2]	2	100.0- 99.8	27	16	7	16.7[6]	17.3[7]	— 0.6	15.0	0.86	0.40	....	....	0.49	Beef Extract.			0.064	...
Period VII[4]	5	100.4-103.8	56	25	25	12.6	9.4	+ 3.2	7.5	0.44	0.00	0.58	7.2	0.17[1]	0.98	12.1	72.7	0.072	6.9
Period VIII	4	101.8-103.4	58	31	22	10.8	8.7	+ 2.1	6.9	0.44	....	0.75	11.0	0.15[1]	0.64	9.4	70.0	0.079	6.9
Period IX	8	104.2-104.8	38[8]	16[8]	18[8]	11.4[8]	15.0[9]	— 3.6[9]	12.9[10]	0.56[11]	....	1.02	8.0	0.33[1]	1.50	11.5	73.3	0.066	8.7
Period X	6	104.0-102.4	42	17	19	13.5	13.6	— 0.1	11.6	0.51	....	1.07	9.2	0.30[1]	0.96	8.5	72.4	0.071	8.0
Period XI	8	102.4-100.0	82	38	37	17.9	11.3	+ 6.6	8.6	0.40	....	0.77	9.0	0.24[1]	1.07	12.4	72.5	0.055	6.2
Period XII	5	99.6-100.2	70	46	16	20.4	13.6	+ 6.8	10.5	0.36	....	0.67	6.4	0.24[1]	0.79	7.5	80.4	0.050	5.6
Period XIII	5	100.4- 99.6	105	45	50	28.7	13.0	+15.7	8.7	0.36	....	0.60	6.9	0.22[1]	0.72	8.3	78.1	0.042	5.5
Period XIV	3	100.6-100.2	70	45	13	28.2	19.5[12]	+ 8.7	15.3	0.41	0.00	....	....	0.23[1]	....	....	....	.....	6.0
Period XV	4	100.0- 99.2	65	45	12	20.4	16.3	+ 4.1	13.3	0.36	0.01	0.55	4.0	.... 0.24[1]	....	....	....	0.051	... 5.2

1. Determined in "composite urines" representing periods.
2. First two days of period excluded from averages for nitrogen balance and food.
3. First day of period excluded from average for excretion.
4. First day of period excluded from averages for nitrogen balance and food.
5. Beef extract period. Note high kreatinin, kreatin and uric acid.
6. 5.3 gm. of this N. was in form of beef extract.
7. Excretion of last day of period. 60 gm. beef extract were given on each of the two days.
8. Average of last three days.
9. Average of two of the last three days—urine of other day lost. Patient at times incontinent.
10. Average of five days of period. Urine of other days lost.
11. Average of four days—beef extract day excluded.
12. Excretion of last day used for nitrogen balance. Total N. of urine (15.3 gm.) + 15 per cent. of food-nitrogen (4.2 gm.).
13. In Period VIII the feces were collected and found to contain 1.8 gm. N. per day. "Excretion" of other periods=total N. of urine + 15 per cent. of food-nitrogen.

In Period VII, coincident with the beginning of a relapse, the carbohydrate food was again increased and, during the next nine days of fever (VII and VIII), the subject gained nitrogen each day, the diet equaling 56 and 58 cal. per kg. and 12.6-10.8 gm. nitrogen. Here, again, it seems very clear that we wholly prevented any febrile loss of body protein.

In Period IX the patient's condition became more serious and we were able to give only a moderate amount of food, 38 cal. per kg. and less. The consequent great disproportion between the decreased food-supply and the probably increased demand for energy or increased intensity of the katabolic processes resulted in very considerable losses of body nitrogen (3 to 10 gm. daily). That the loss was not even greater seems surprising, and is probably to be explained by the known tendency of the organism to react less violently to such a stimulus in the later stages of a long illness.

This same tendency probably explains the fact that during the next period (X), with the temperature still above normal, nitrogen equilibrium was attained on almost the same diet.

On further increasing the value of the food to 82 cal. per kg. (XI) there was an average plus balance of 6.6 gm. nitrogen per day, though the maximum temperature on four days was above 101 F.

During the remainder of the experiment the temperature was normal and the excessive katabolism observed during the febrile reaction had given place to the increased anabolism characteristic of convalescence. Food of high protein content and equivalent to *70 (XII), 105 (XII), 70 (XIV) and 65 (XV) cal. per kg. resulted in the large average daily plus balances of 6.8, 15.7, 8.7 and 4.1 gm. nitrogen.*

A comparison of Periods XIII and XIV shows the great value of carbohydrate in assisting the gain of protein in convalescence, which is not wholly in accord with the idea of Benedict and Surànyi, that the nitrogen retention in convalescence is largely independent of the fuel value of the food.

A comparison of Periods II and VIII again illustrates the importance of the intensity of the katabolic process in determining the degree of sparing of body protein to be accomplished by any diet. The intensity of the katabolism does not always go parallel to the temperature, as has been pointed out by Kraus and others. In both of the above periods the maximum temperature was about the same, and the food differed only slightly.

	Cal. Per Kg				
Food.	Total.	Fat.	C. H.	N. Gm.	N. Bal.
Period II.....	54	14	36	7.7	−2.2
Period VIII.....	58	31	22	10.8	+2.1

TABLE 29.—PATIENT S, P—S: DAILY FOOD AND ANALYSES OF URINE

Insufficient food-supply throughout. Great loss of body protein. Great emaciation.

Day of Disease.	Temp. F. High.	Temp. F. Low.	Urine: Volume. c.c.	Urine: Total N.	Urine: NH_3 N.	Urine: Kreatinin N.	Urine: Kreatin N.	Urine: Uric Acid N.	Urine: "Rest" N.	Per Cent. of Total N.: Urea.	Per Cent. of Total N.: NH_3	Per Cent. of Total N.: Rest.	Remarks.
12	104.0	103.0	1280	22.7	1.61	0.54	0.71	0.17	1.56	80.0	7.1	6.9	*
13	103.5	102.4	1280	22.7	1.61	0.54	0.71	0.17	1.56	80.0	7.1	6.9	*
14	103.4	102.0	1350	22.4	1.80	0.54	0.67	0.19	1.07	81.0	8.0	4.8	*
15	103.5	102.0	860	....	....	0.35	0.34	0.11	....	....	7.9	....	*
16	103.4	102.0	1240	18.7	1.65	0.52	0.48	0.19	1.62	76.3	8.8	8.7	
17	103.4	101.0	1040	14.8	1.38	0.43	0.31	0.13	1.29	76.1	9.3	8.7	*
18	104.4	99.0	1300	20.8	1.84	0.54	0.57	0.21	1.72	76.7	8.9	8.3	
19	103.0	102.0	....	....	....	....	....	....	....	....	....	....	
20	103.0	103.0	950	13.8	0.97	0.37	0.38	0.11	1.24	77.0	7.8	9.0	
21	103.6	101.0	1140	14.7	1.44	0.43	0.37	0.07	1.32	75.3	9.8	9.0	*
22	104.0	102.4	1150	15.9	1.47	0.49	0.35	0.11	....	....	9.2	....	
23	104.0	100.0	....	....	....	....	....	....	....	....	....	....	
24	105.6	102.8	920	10.2	1.10	0.35	0.22	0.08	0.94	73.7	10.8	9.2	
25	104.4	103.4	....	....	....	....	....	....	....	....	....	....	
26	103.6	101.0	....	11.7?	1.44	0.51	0.17	0.13	1.62	66.9	12.4	13.9	*
27	103.4	102.0	....	8.0?	....	0.50	0.18	0.12	1.62	61.2	14.1	16.5	*
28	102.6	101.0	....	....	....	....	....	....	....	....	....	....	
29	103.0	100.0	....	....	....	....	....	....	....	....	....	....	
30	103.0	100.6	900	15.4	1.17	0.31	0.26	0.08	0.87	82.5	7.6	5.6	
31	103.0	101.0	1380	18.5	1.36	0.42	0.38	0.14	1.36	80.2	7.4	7.4	*
32	102.6	99.6	....	....	....	....	....	....	....	....	....	....	
33	102.6	99.6	1500	13.9	1.30	0.26	0.20	0.13	0.75	81.4	9.3	5.4	
34	103.6	101.8	2180	13.7	....	....	....	....	....	....	....	....	
35	102.0	100.4	1800	12.7	1.02	0.18	0.12	0.10	1.09	80.4	8.0	8.6	
36	103.0	99.0	800	8.8	0.61	0.18	0.15	0.07	1.15	75.6	6.9	13.1	
37	103.0	100.0	1800	....	....	....	....	....	....	....	....	....	
38	102.4	99.0	1960	....	....	0.30	....	....	....	....	....	....	
39	102.4	99.0	....	....	....	....	....	....	....	....	6.0	11.0	
40	102.4	99.6	1400	14.8	0.84	0.37	0.02	0.12	1.66	....	5.7	11.2	*
41	103.0	99.6	1320	14.2	0.66	0.42	....	0.12	1.17	83.4	4.6	8.2	*
42	103.0	101.0	1580	12.3	0.80	....	....	0.07	....	....	....	....	
43	103.4	100.6	1260	10.9	0.68	0.25	0.03	0.09	0.89	81.6	6.2	8.2	
44	104.4	100.4	750	10.5	0.74	0.28	0.00	0.08	1.04	79.6	7.0	9.9	*
45	103.8	101.6	540	....	....	....	....	....	....	....	7.9	9.3	
46	102.4	100.4	630	8.5	0.60	0.23	0.07	0.06	0.72	80.1	7.0	8.5	
47	104.4	100.4	520	6.0	....	....	0.03	0.04	0.56	80.3	8.1	8.3	
48	104.0	102.0	1360	14.7	1.01	0.27	....	0.07	1.34	81.8	6.8	9.1	*
49	103.0	100.0	620	7.2	....	....	0.00	0.05	....	....	3.4	8.8	Wt. 42 Kg.
50	103.0	101.0	730	9.6	0.71	0.27	....	0.07	0.85	80.3	7.3	8.8	*
51	103.0	100.0	390	....	....	....	....	0.04	....	....	8.2	7.8	
52	104.4	101.0	570	....	....	....	....	0.09	....	....	7.4	8.9	
53	103.0	101.0	570	10.0	0.73	0.28	....	0.09	....	....	7.3	....	*
54	102.4	100.0	930	10.0	0.73	0.28	....	0.09	....	....	7.3	....	*
55	103.0	100.0	1180	12.7	....	0.22	....	....	....	....	....	....	*
56	102.4	100.0	670	6.8	....	0.22	....	0.06	....	....	....	....	
57	103.0	99.0	890	9.9	....	....	....	....	....	....	....	....	
58	100.8	98.4	....	....	....	....	....	....	....	....	....	....	

* Many of the urines of this patient were incomplete; those which are known to be complete are marked with a *.

The difference in the nitrogen balance of these periods must be, in large part, due to the difference in intensity of the katabolic processes.

THE NITROGEN PARTITION OF THE URINE IN TYPHOID FEVER

In addition to the data on this topic contained in the experiments already described, results from the analyses of the urine in three other severe cases are given in Tables 29, 30 and 31.

Patient 8.—P—s, aged 31, admitted the tenth day of the disease. Positive blood-culture. Illness very severe. Duration of temperature sixty-seven days. Complicated by intestinal hemorrhage. Marked emaciation.

Patient 9.—O—y, laborer, aged 21, poorly nourished, admitted the sixth day of the disease. Blood culture positive. Illness severe. Duration of fever twenty-eight days. Complicated by cholecystitis, without jaundice, and furunculosis. Emaciation during the illness marked.

Patient 10—E. K—r, lithographer, aged 15, admitted the eighth day of the disease. Positive blood culture. Illness moderately severe. Duration of fever twenty-one days, followed by a relapse. Complication, otitis media.

Kreatinin.—From the work of Folin[34] and others[35] we know that in health the amount of this substance excreted is independent of the total amount of protein katabolized, and is practically constant from day to day, and from hour to hour. It has been further shown that the amount excreted by different individuals bears a definite relation to the weight,[34] muscular development and strength[36] of those individuals. Kreatinin is essentially a product of endogenous metabolism,[34] but is not a measure of the total endogenous metabolism.[36] The truth of the latter statement is well shown by the kreatinin excretion by subjects of typhoid fever. With the increased katabolism of fever there is usually an increase in the amount of kreatinin excreted, as has already been shown by Leathes,[37] but by no means in proportion to the total amount of the body protein katabolized. In considering the question of an increase or decrease of kreatinin excretion we must not base any conclusion on the absolute amount excreted, because of the great normal variations in different individuals; but must consider the relative amount per kg. of body weight. The highest relative excretion of kreatinin observed during these experiments is 10.6 mg. kreatinin-nitrogen per kg., the "kreatinin-coefficient" of U-h (Experiment 2, Period I, see Table 8), at which time the subject was losing about 9 gm. of nitrogen per day, and his total

34. Folin: Am. Jour. Physiol., 1905, xiii, 83.
35. Klercker: Biochem. Ztschr., 1907, iii, 46. Hoogenhuyze and Verploegh: Ztschr. f. physiol. Chem., 1905, xlvi, 415. Shaffer: Am. Jour. Physiol., 1908, xxii, 445.
36. Shaffer: Am. Jour. Physiol., 1908, xxiii, 1.
37. Leathes: Jour. Physiol., 1907, xxxv, 205.

TABLE 30.—PATIENT 9, O—Y: DAILY FOOD AND ANALYSES OF URINE

Weight about 50 Kg.

Average Daily Food and Nitrogen Balance.	Day of Disease.	Temp. F. High.	Temp. F. Low.	Urine Volume. c.c.	Urine Total N.	Urine NH_3 N.	Urine Kreatinin N.	Urine Kreatin N.	Urine Uric Acid N.	Urine "Rest" N.	Per Cent. of Total N. Urea.	Per Cent. of Total N. NH_3	Per Cent. of Total N. Rest.
					PERIOD I								
34 Cal. per kg.	9	105.0	103.0	2170	13.9	11.3	0.45	....	0.18	1.04	79.1	8.2	7.5
11.1 gm. N.	10	104.6	102.0	3110	28.4	....	0.73	0.28	0.14	2.07	....	...	9.5
Bal. = — 6.7	11	104.0	102.4	1200	13.1	0.76	0.36	0.14	0.14	0.77	83.5	5.6	5.9
	12	104.4	102.6	1080	9.1	0.58	0.28	0.11	0.10	....	....	6.3	...
					PERIOD II								
39 Cal. per kg.	13	105.0	102.4	1200	17.1	0.87	0.47	0.22	0.20	0.88	84.5	5.1	5.1
6.8 gm. N.	14	104.2	103.0	1960	16.1	1.03	0.46	0.19	0.21	0.50	85.1	6.4	3.1
N. Bal. = — 10.3	15	104.3	102.0	1320	15.0	0.81	0.47	0.22	0.22	0.89	82.7	5.4	5.9
	16	104.4	103.0	1170	16.0	0.79	0.47	0.27	0.25	0.49	86.0	5.0	3.1
					PERIOD III								
46 Cal. per kg.	17	104.2	102.0	1050	9.6	0.47	0.29	0.18	0.15	0.38	84.7	4.9	4.0
4.4 gm. N.	18	104.8	102.6	....	....	....	....	....	....	....	....	....	....
N. Bal. = — 5.4	19	104.8	101.0	1500	9.6	0.49	0.31	0.16	0.16	0.63	81.9	5.1	6.5
	20	103.6	99.0	1340	8.3	0.49	0.26	0.12	0.13	0.46	82.3	6.0	5.5
					PERIOD IV								
47 Cal. per kg.	21	103.4	99.0	700	8.8	0.34	0.31	0.10	0.16	0.55	83.7	3.8	6.2
9.8 gm. N.	22	103.8	99.0	400	....	....	....	....	....	....	83.3	5.4	5.4
N. Bal. = — 4.6	23	101.8	99.0	620	13.0	0.54	0.36	0.18	0.13	0.59	87.3	4.2	4.5
	24	102.0	98.2	1000	12.7	0.59	0.36	0.19	0.13	1.03	83.0	4.7	8.1
					PERIOD V								
40 Cal. per kg.	25	101.4	98.4	1080	10.8	0.52	0.34	0.15	0.11	0.92	81.2	4.9	8.5
10.1 gm. N.	26	102.0	98.0	740	....	....	....	....	....	....	84.8	4.5	5.6
N. Bal. = — 1.5	27	101.4	98.4	950	9.4	0.40	0.30	0.14	0.08	0.57	84.2	4.3	6.0
	28	100.2	99.0	800	9.9	0.40	0.30	0.11	0.08	0.41	86.9	4.0	4.1

TABLE 31.—PATIENT 10, K—R: DAILY FOOD AND ANALYSES OF URINE

Weight about 50 Kg.

Average Daily Food and Nitrogen Balance.	Day of Disease.	Temp. F. High.	Temp. F. Low.	Urine Volume. c.c.	Urine Total N.	Urine NH_3 N.	Urine Kreatinin N.	Urine Kreatin N.	Urine Uric Acid N.	Urine "Rest" N.	Per Cent. of Total N. Urea.	Per Cent. of Total N. NH_3	Per Cent. of Total N. Rest.
					PERIOD I								
	13	104.0	102.0	1020	17.4	0.88	0.47	0.11	0.10	1.17	84.5	5.1	6.8
	14	103.4	101.4	....	....	....	....	....	....	....	....	....	....
97 gm. Fat	15	102.0	99.0	1060	15.2	1.14	0.44	0.02	0.13	1.35	79.8	7.5	8.9
468 gm. C. H.	16	103.0	99.0	420	....	....	....	....	....	....	....	....	....
8.5 gm. N.	17	102.4	99.4	840	12.0	1.06	0.46	0.10	0.13	0.98	77.3	8.8	8.2
60 Cal. per kg.	18	103.4	100.0	900	10.0	0.93	0.45	0.11	0.13	1.28	71.0	9.3	12.8
N. Bal. = — 6.4	19	102.4	99.0	1800	....	....	....	....	....	....	....	....	....
per day.	20	100.0	99.0	.....	....	....	....	....	....	....	76.1	7.3	11.7
					PERIOD II								
Normal Temperature.													
	1	99.4	98.4	1360	12.2	0.71	0.45	0.18	0.12	1.14	78.7	5.8	9.3
	2	99.4	98.4	....	....	....	....	....	....	....	....	....	....
118 gm. Fat	3	98.8	98.4	975	10.8	0.72	0.36	0.19	0.10	1.12	77.0	6.7	10.4
463 gm. C. H.	4	99.8	98.0	1350	9.4	0.57	0.33	0.17	0.05	0.97	77.9	6.1	10.4
9.3 gm. N.	5	100.0	98.0	1100	9.1	0.50	0.34	0.14	0.09	0.85	79.1	5.5	9.3
65 Cal. per kg.	6	100.4	98.0	1110	8.6	0.45	0.34	0.13	0.08	0.66	80.2	5.3	7.7
N. Bal. = — 1.9	7	100.0	98.0	1110	8.6	0.45	0.34	0.13	0.08	0.66	80.2	5.3	7.7
	8	99.2	98.2	....	....	....	....	....	....	....	....	4.6	9.5
					PERIOD III								
Relapse.													
	1	101.4	99.0	1650	9.7	0.48	0.35	0.14	0.07	0.90	80.0	5.0	9.3
	2	103.4	100.0	1300	9.5	0.50	0.37	0.13	0.09	1.00	78.3	5.2	10.5
128 gm. Fat	3	104.0	99.2	930	7.2	0.74	0.27	0.06	0.07	0.85	72.3	10.3	11.8
510 gm. C. H.	4	104.6	102.0	1125	10.2	0.46	0.43	....	0.10	0.83	82.3	4.5	8.2
8.9 gm. N.	5	104.4	102.0	910	11.7	0.57	0.51	....	0.12	1.35	78.1	4.9	11.6
70 Cal. per kg.	6	102.0	100.4	1480	8.0	0.62	0.37	0.00	0.08	1.34	69.9	7.8	16.8
N. Bal. = — 2.0	7	100.6	98.6	1220	10.5	0.81	0.40	0.00	0.12	....	....	7.7	....
					PERIOD IV								
Convalescence.													
	1	99.6	98.4	960	12.3	0.98	0.44	....	0.13	....	....	....	....
	2	99.0	98.4	1230	8.0	0.72	0.32	....	0.10	....	....	....	....
156 gm. Fat	3	99.6	98.4	1390	7.3	....	0.32	....	....	....	....	....	....
540 gm. C. H.	4	99.0	98.4	1675	....	....	....	....	....	....	....	....	....
13.2 gm. N.	5	100.0	97.9	1640	11.4	....	0.34	....	0.11	....	....	....	....
80 Cal. per kg.	6	100.0	97.4	860	....	....	....	....	....	....	....	....	....
N. Bal. = + 1.4													

endogenous katabolism was therefore greatly increased. The normal kreatinin-coefficient of this subject, a laborer, was certainly not less than 9, which gives a probable increase of less than 20 per cent. in the kreatinin excretion at the height of the fever. The other experiments show in general the same rule: a marked, though relatively rather slight, increase during the height of the fever. This increase is very clearly shown by those patients who suffered a relapse (see Tables 15, 24 and 28). With, or even before the fall in the temperature, there is a progressive decline in the kreatinin excretion, this decrease apparently going somewhat parallel with the lowered muscular strength of the individual, although the kreatinin-coefficient does not usually fall so low as is often seen in subjects of chronic diseases.[38]

The lowest relative kreatinin excretion observed in these subjects were about 4 and 5 mg. kreatinin-nitrogen per kg., found late in the disease with P——s (Table 29) and G——t (Table 28) respectively; and these were the patients who suffered the longest and most severe illnesses of the series.

In order to gather more accurate data from these patients regarding the relation between muscular strength and the amount of kreatinin excreted, a few measurements with a hand dynamometer were made on seven days early in convalescence on W——d, G——t, and B——t.

Five tests with two-minute intervals were made with each hand on each day. These tests were made after the end of the experiments and the kreatinin excretion at the time is not known, but the latter had probably not greatly changed from the values found in the last period of the respective experiments, and these values are therefore used in the accompanying comparison. The readings of the dynamometer are given in kilos.

While the tests with such an instrument are not very exact, and allow us to judge the strength of only one set of muscles, the results are fairly satisfactory and show very strikingly that the strongest subject excreted relatively the most kreatinin.[39]

The increase of kreatinin excretion during the height of the fever, as has already been pointed out by one of us,[40] is an exception in the relationship of kreatinin to muscular development; but, aside from this exception, the amount of kreatinin excreted per kg. of body weight runs parallel with the "muscular efficiency" of the individual.

---

38. Shaffer: Am. Jour. Physiol., 1908, xxiii, 1.

39. For making the tests with the dynamometer we are indebted to Dr. E. S. Bishop, Junior Physician on the second Medical Division of Bellevue Hospital.

40. Shaffer: Am. Jour. Physiol., 1908, xxiii, 10.

TABLE 32.—PATIENT 7, G—T: MEASUREMENTS WITH HAND DYNAMOMETER *

Day of Convalescence						
27	29	31	32	33	34	35
			Right Hand			
Kg.	Kg.	Kg.	Kg.	Kg.	Kg.	Kg.
18	21	20	22	20	22	25
19	18	20	20	22	23	22
18	20	21	20	21	21	20
18	20	18	20	21	23	23
18	20	21	22	22	23	23
			Left Hand			
18	20	19	18	18	18	20
17	17	20	18	18	19	18
18	20	17	18	19	21	18
15	18	18	19	21	18	20
17	20	19	20	21	21	20
—	—	—	—	—	—	—
			Average			
17.6	19.4	19.3	19.7	20.3	20.9	20.9
			Average of all Readings			
..	..	..	19.7	..	..	..
			Kreatinin Coef.			
..	..	..	5.2	..	..	..

* Test began ten days after the end of experiment.

TABLE 33.—PATIENT 4, W—D: MEASUREMENTS WITH HAND DYNAMOMETER *

Day of Convalescence						
11	13	15	16	17	18	19
			Right Hand			
Kg.	Kg.	Kg.	Kg.	Kg.	Kg.	Kg.
25	20	25	27	30	30	30
27	23	27	27	32	32	34
27	27	27	28	31	31	34
25	25	29	26	28	30	32
23	27	23	29	31	30	32
			Left Hand			
23	15	23	21	28	27	28
23	17	21	24	29	28	27
24	16	24	25	27	27	26
22	21	25	21	28	24	25
18	18	23	25	23	24	25
—	—	—	—	—	—	—
			Average			
23.7	20.9	24.7	25.3	28.7	28.3	29.3
			Average of all Readings			
..	..	..	25.8	..	..	..
			Kreatinin Coef.			
..	..	..	7.0	..	..	..

* Tests began three days after end of experiment.

Kreatin.—The behavior of this substance in typhoid fever has already been referred to. It is excreted in large amounts at the height of the disease if the subject is losing large quantities of body protein (see Table 29, the subject of which lost much body nitrogen throughout the greater part of the experiment). We believe that the kreatin excreted under such circumstances is directly derived from muscle tissues, and that its appearance in the urine indicates that muscle tissues are being destroyed.

TABLE 34.—PATIENT 5, B—T: MEASUREMENTS WITH HAND DYNAMOMETER

Day of Convalescence				
11	13	15	16	17
		Right Hand		
(28)	39	41	35	41
37	37	36	40	43
36	40	40	43	44
41	35	39	39	44
37	33	40	42	40
		Left Hand		
36	35	37	36	41
35	28	34	40	38
38	30	35	37	37
36	31	35	38	38
34	30	37	36	39
		Average		
36.7	33.8	37.4	38.6	40.5
		Average of all Readings		
..	..	37.4	..	..
		Kreatinin Coeficient *		
..	..	8.3	..	..

* Average of last ten days of Period V=0.615 gm. Kreatinin—N. Divided by 74 Kg.=8.3

Uric Acid.—Except for a few instances, the diets used contained no purins, and we are therefore concerned only with endogenous uric acid. Our results show as a rule a marked increase in the excretion of this substance during the height of the fever, followed usually by a decline with the fall of the temperature. The amount excreted varies with different individuals and each experiment should be considered by itself. With some of the subjects the uric acid remained high well into convalescence (Tables 28 and 29), while with others it fell in convalescence to probably below the normal (Tables 8, 29 and 30). The high uric acid excretion during the fever is in accord with the observations of Leathes[37] and others.

Xanthin Bases.—A. R. Mandel[41] has determined the amount of xanthin bases excreted by three subject of surgical fevers and by one subject

41. Mandel: Am. Jour. Physiol., 1904, x, 452; ibid, 1907, xx, 439.

of pneumonia, and finds a maximum of about 60 mg., calculated as xanthin, in twenty-four hours, as compared with the probable normal of about 20 or 30 mg. On the basis of these results, together with the fact that a rise in temperature follows the injection or ingestion of xanthin bases, Mandel apparently concludes that substances of this nature are primarily responsible for the febrile temperature. We can scarcely agree with this view. According to our results the excretion of xanthin bases bears no constant relation to the height of the temperature. With Z——o, for instance (Table 12), the xanthin increases with the slow fall in the temperature, the reverse of Mandel's finding. With B——t (Table 20) the same is true except that the highest amount (81 mg.) was excreted during the relapse. With L——d (Table 24) there is little difference between the periods of fever and of normal temperature. With W——d (Table 16) the highest amount, 91 mg. xanthin, is found at the height of the disease, but the lowest, 30 mg., appears during a relapse when the temperature was moderately high.

Most of our results are abnormally high, according to Mandel's standard,[42] but are not high when compared with the results of Camerer.[43]

We find no evidence in our experiments that the xanthin bases are increased in typhoid fever or that the amount excreted bears any constant relation to the febrile temperature, thus failing to confirm either Erben[44] or Mandel.

Urea, Ammonia and "Rest" Nitrogen.—Folin[46] has shown that for the judgment of the normality or abnormality in the excretion of these substances, or "fraction" in the case of the "rest nitrogen," it is necessary to consider the amount of total nitrogen excreted. Table 35 contains the normal limits, compiled from the results of Folin and of one of us, for the excretion of these substances. The figures are based on the analyses of about 200 urines from a large number of normal persons. On the basis of these standards it is rather surprising that we do not find any very marked deviations from the normal in these subjects of typhoid fever. There are many instances in each experiment of increased excretion of ammonia and "rest" nitrogen, but the increase is rarely great, and not at all comparable to the figures obtained by Ewing and Wolf in the toxemias of pregnancy and allied conditions. On the whole our results justify the conclusion that during the height of the disease or during a relapse there is usually a slightly higher "rest" nitrogen and

42. Morganbesser: Cited by Mandel.
43. Camerer: Ztschr. f. Biol., 1891, xxviii, 72.
44. Erben: Ztschr. f. Heilk., 1904, xxv, 33.
45. Folin: Am. Jour. Physiol., 1905, xiii, 66.

ammonia excretion than is found either normally or in the less active stages of the disease, but that the differences are usually not great enough to warrant the belief that the urea-forming process is necessarily seriously interfered with in uncomplicated typhoid fever.

The almost, if not quite, normal urea and "rest" percentages at times when the subjects were losing much body protein-nitrogen are especially instructive in showing that the protein of body tissue is at least under these conditions katabolized in the same way as food protein.[46] (See Table 8, Periods I and III; Table 12, Period III; Table 20, Periods I, II, etc.).

TABLE 35.—PROBABLE NORMAL LIMITS IN THE EXCRETION OF UREA, AMMONIA AND "REST" N.

Gms. of Total Nitrogen.	Per Cent of Total Nitrogen					
	Urea		Ammonia		"Rest"	
	Low.	High.	Low.	High.	Low.	High.
3 to 5.9	56	79	4	13	4	15
6 to 9.9	72	85	2	7	5	10
10 to 14.9	80	89	2	6	4	9
15 to 22	85	90	2	5	2	7

We should, of course, not conclude from our results that one never finds in typhoid fever very marked abnormalities in the excretion of urea and rest nitrogen. Ewing and Wolf[47] have found low urea and high "rest" nitrogen percentages in fatal cases. We have had no fatal cases in this series, though many of the subjects were severely ill. From the fact that most of our subjects did not show a very marked increase in "rest" nitrogen or decrease of urea percentage we are led to the conclusion that a serious interference with the urea-forming function is not an essential part of the process of typhoid fever, and that, when such marked abnormalities of this function appear in this disease, as found by Ewing and Wolf, they are the result of factors complicating the disease. And by such complicating factors we mean not the common accidents, like intestinal perforation, but rather a serious damage to the liver or other

46. The truth of the above statement depends, of course, on the reliability of the methods for the determination of urea. The Folin method, which we believe is superior to other methods at present used, has been employed in these experiments and in all other recent work in this laboratory. This, like other urea methods, is, however, an indirect one, and is based on the assumption, proved by Folin for normal urines, that no substance other than urea is present which may be decomposed, with the formation of ammonia, under the conditions of the determination; and we should not overlook the possibility that in fever or other pathological urines such substances may be excreted.

47. Ewing, J., and Wolf, C. G. L.: The Clinical Significance of the Urinary Nitrogen: III. Nitrogenous Metabolism in Typhoid Fever, THE ARCHIVES INT. MED., 1909, iv, 330.

important organs, perhaps involving cellular degenerations, and thus interfering with the functions of those organs.

The ammonia excretion in these experiments was usually somewhat increased during the active stages of the disease, this increase being on the whole greater than the increase of "rest" nitrogen. The high ammonia is probably coincident with an increased excretion of organic acids; diacetic and oxybutyric acids were never found, even at those times when the subjects were not receiving much carbohydrate. The amount of ammonia was moreover never large enough to indicate any considerable acidosis. The ammonia excretion in these subjects does not appear to have been affected by the intake of carbohydrate, as it would be in the presence of an oxybutyric acid acidosis.

THE SULPHUR PARTITION OF THE URINE IN TYPHOID FEVER

Total Sulphur.—Since the sulphur of the urine is derived chiefly from food or tissue protein the amount of total sulphur excreted usually bears a fairly constant relation to the amount of total nitrogen of the urine. As might be expected this relation varied somewhat with different diets. With a milk-egg diet, with or without meat, between 7 and 8 parts of total sulphur are excreted for each 100 parts of total nitrogen.[48] The same relationship was found in the urine of these subjects of typhoid fever, whether they were losing body protein or retaining food protein. The ratio between total sulphur and total nitrogen was with W——d (Table 16) 7.5 when he was losing 11.3 gm. of body-protein nitrogen per day and 7.3 when he was gaining 3.7 gm. nitrogen per day. Much the same thing is seen with Z——o and B——t (Tables 12 and 20). The ratios are in several instances below 7, but are, on the whole, remarkably constant.

The fact that an equivalent amount of sulphur is excreted with the nitrogen, even when the subject is losing body protein, is of interest in showing that the effect of carbohydrate in decreasing the nitrogen excretion in fever is not to be explained by a mere temporary retention of amino-acids of the food protein in the form of amino-sugars (Lüthje[49]). Were this the case we should expect, on withdrawing the protecting carbohydrate, a sudden excretion of the retained nitrogen without an accompanying amount of sulphur.[50] On withdrawing the carbohydrate from Z——o (Tables 11 and 12) in Period III the nitrogen excretion

48. Folin and Shaffer: Am. Jour. Physiol., 1902, vii, 145. Folin: Am. Jour. Insanity, 1904, lx, 729. Shaffer: Am. Jour. Physiol., 1908, xxii, 449.

49. Lüthje: Verhandl. d. Kongress f. inn. Med., 1906, xxiii, 440.

50. Unless the nitrogen were retained in some form of thio-amino-sugar.

increased over 50 per cent., and the total sulphur increased practically in proportion. In Periods I and II, when there was great protection from the febrile loss of body nitrogen, the nitrogen-sulphur ratios were normal, again indicating that the body protein was actually protected from taking part prominently in the febrile katabolism. Had the carbohydrate caused merely a retention of amino-acids this ratio might well be abnormally high.

Ethereal Sulphur.—This fraction of the sulphur excretion by our subjects was within the normal limits, usually between 0.02 and 0.07 gm. This fact and the usual absence of a large excretion of indican gave no indication of excessive intestinal putrefaction.

Neutral Sulphur.—This fraction of the sulphur partition was uniformly much increased above the accepted normal values of 0.10 to 0.15 gm.[51] The highest amounts were excreted during the height of the fever, and fell to within normal limits with the decline of the temperature. The amount of neutral sulphur excreted in this disease bears no constant relation to the total sulphur, to total nitrogen, or to the loss of body-protein-nitrogen, and the significance of the febrile increase in this fraction is not at present clear.

Subjects of fever are supposed to be especially prone to alimentary glycosuria; and we rather expected to find a considerable excretion of sugar during the times when our patients were taking large quantities of lactose and other carbohydrates. Small quantities of sugar, rarely more than traces, were occasionally found in the urines during these experiments. The amounts were not large enough for accurate determination by titration with Fehling's or Pavy's solutions, and probably never exceeded 0.2 per cent., or a maximum of about 6 gm. in twenty-four hours.

THEORETIC CONSIDERATIONS

We have seen on a number of occasions in the preceding pages that, during the active stages of the disease, *a loss of body protein may be wholly prevented* by the intake of food of sufficient caloric value. These instances show very conclusively that the febrile destruction of body protein, including *both the effect of pyrexia and of toxins,* in the human subject of typhoid fever, may be either prevented altogether *or* may be compensated for by a large retention of body protein. As stated earlier in this paper, other experiments have indicated that the effect of pyrexia in causing an increased katabolism of protein may be prevented, but so far as we know the experiments here recorded are the first to show satis-

51. Shaffer: Am. Jour. Physiol., 1906, xvii, 369-375; ibid, 1908, xxii, 449.

factorily in the human subject that the action of toxins, as well as of the pyrexia, may be prevented from causing a loss of body protein by the addition to the food of a sufficient quantity of carbohydrate.

What is the probable explanation of this sparing of protein by carbohydrate in fever? Do we, by food of high caloric value, actually retard or prevent the febrile destruction of the body protein, or do we cause an increased retention of food protein which masks the destruction of body protein?

This very important question we, of course, do not hope to answer conclusively in this paper, but certain of our results have a very direct bearing on this consideration.

Results based wholly on the comparison of the intake and excretion of nitrogen, the nitrogen balance, show merely the final gain or loss of nitrogen to the body; they do not show variations in the extent of the endogenous metabolism; they do not tell us the amount of body protein destroyed in fever any more than they tell us the amount of protein destroyed in the normal endogenous katabolism. The nitrogen balance in our experiments shows that the loss of protein in fever becomes less or may be prevented by food of high carbohydrate value. We might interpret this in at least two ways: that the large food-supply causes merely a retention of food protein or other nitrogenous substances, thus masking the destruction of body protein; or that the large food-supply has furnished all of the required energy and in available form to maintain equilibrium, and that the body found it no longer necessary to use its own material for that purpose.

Should we accept the idea of Krehl of an actual destruction of the protein of body cells by bacterial toxins we must also accept the first explanation of our result, because it is improbable that such a toxic destruction can be prevented by any form or amount of food. But Krehl's idea of the toxic destruction has by no means been proved to be correct, and there is one point brought out in our experiments and already referred to which we think distinctly favors the other interpretation—i. e., that the chief effect of the large carbohydrate intake is actually to protect the body protein from taking part in the excessive katabolism. This point is the behavior of the kreatin excretion. We have already considered this matter in some detail and need not repeat it here further than to say that endogenous kreatin, so far as we know, is excreted only when there is an abnormal absorption of muscle protein; that we have found it excreted in large amounts by the subjects of our experiments when they were at the same time losing much body protein; *and that it was not excreted*, or at any rate in but small amounts, *when*

the same subjects were being protected from the loss of body protein by food of high caloric value and rich in carbohydrates. It therefore seems very probable that such food in some way greatly retards and, if sufficient, may even prevent the "toxic" or other destruction of muscle protein.

The relative constancy of the relationship between total nitrogen and total sulphur, which has already been referred to, is another indication of the same character.

Whether the above conclusion is wholly sound, further work will have to determine. It may well be that there remains a relatively small effect of toxins on the protein katabolism which may not be influenced by food, for, as we have seen, small amounts of kreatin were often excreted when the subjects received a very large supply of food and when they were even gaining nitrogen. Kreatinin, uric acid, and neutral sulphur are usually high during the active stages of the disease, whether or not the food value is high, and the endogenous katabolism concerned with these substances may be independent of the food supply. But we believe our results show that *quantitatively the most important part of the febrile destruction of body protein (in typhoid) may be retarded or prevented by food containing a moderate amount of protein and very rich in carbohydrate.*

The total caloric value of the diets used in the periods of great protection of body protein is very high, 60 to 90 cal. per kg. Whether such large amounts of food were actually utilized within the organism it is impossible to learn from our data. We have had no facilities for determining the total energy exchange, but, from the few such determinations which have been made on fever subjects, it is perhaps improbable that the total heat production of our patients reached the values represented by the larger amounts of food.

It seems to us more probable that the carbohydrate is the essential constituent of the food, and that the same sparing of body protein might have been accomplished had the fat been withdrawn from the various diets. The basis for this opinion is, however, not wholly satisfactory, for the data in our experiments regarding the relative value of fat in sparing body protein are not clear. This point awaits further investigation.

If fat does not assist in the protection of body protein from the febrile destruction the sparing observed during these experiments is to be referred to carbohydrate alone. The carbohydrate value of the diets used during the most favorable periods was between 40 and 50 carbohydrate calories per kg., and this amount, or even more, is necessary to pre-

vent wholly a febrile loss of body protein. It may be that in carbohydrate alone we must supply more energy than equals the total heat production; and, if so, the situation is similar to that of the experiment by Murlin,[52] who found that 125 per cent. of the maintenance requirement in the form of carbohydrate, when given to a dog, spared 49 per cent of the starvation excretion of nitrogen, while 100 per cent. of the requirement spared only 23 per cent. of the starvation excretion.

The typhoid subject who is losing body protein (62.5 gm.) equivalent to 10 gm. of nitrogen per day derives from this protein only 250 cal., and it seems very remarkable that, to prevent this loss, we must give him additional carbohydrate equivalent to 2,000 cal. or more. The same is true in simple starvation. In neither instance have we at present any explanation of this apparent anomaly. In both cases it is evident that the use of the carbohydrate is not a mere replacement of isodynamic quantities of protein. Some insight into these questions will doubtless follow investigations of the total energy exchange in fever subjects receiving diets containing varying quantities of carbohydrate. At the present time an adequate explanation of this action of carbohydrate is not possible.

PRACTICAL THERAPEUTIC CONSIDERATIONS

We have so far avoided any discussion of the therapeutic value in typhoid or other acute infectious fevers of the protection from the katabolism of body protein afforded by diets rich in carbohydrates, for the reason that we have not accumulated sufficient data to judge this question. It seems to us obvious that unless there are distinct and forceful objections to such dietetic treatment the subject of the disease will be better off if he is not permitted to use up his body material. Unless we gratuitiously assume the febrile destruction and loss of body protein to be a beneficial process, it is difficult to avoid the conclusion that we are ministering to the welfare of the patient by preventing that destruction or loss. We have so far encountered clinically no valid objection to the use of such diets as those of the experiments here described, and, unless future experience proves such objection, we believe it highly desirable to retard and, if possible, prevent the febrile loss of body protein.

The general nutrition of the subjects of our experiments was exceptionally good at the end of the disease, many weighing more at the time of discharge than when they entered the hospital.

A more detailed discussion of the strictly clinical aspects of this question will be attempted in a future paper.

52. Murlin: Am. Jour. Physiol., 1907, xxi, 254.

CONCLUSIONS

As a result of our experiments the following conclusions may be drawn regarding the protein metabolism in typhoid fever:

1. By the use of diets of high caloric value and especially rich in carbohydrate it is possible to retard and, if the carbohydrate supply be sufficient, to prevent the febrile *loss* of body-protein-nitrogen in subjects of typhoid fever.

2. By such dietetic treatment the "toxic" destruction of body protein as well as the destruction due to simple pyrexia in this disease may therefore be *either prevented or compensated for.*

3. The behavior of kreatin and of total sulphur in our experiments appear to show that the febrile destruction of body protein, including the action of pyrexia and of toxins, is actually retarded or even wholly prevented by the intake of sufficient carbohydrate.

The prevention of the febrile loss of body protein is therefore probably not to be explained by a mere compensatory retention of food protein.

4. The results support the belief that in fever there is a greater need for carbohydrate; that if the food does not contain sufficient carbohydrate the body protein is drawn on perhaps to supply energy in an available form; but that, if sufficient carbohydrate be available from the food, the body protein is protected from the febrile destruction.

5. If, as seems probable from our results, the "toxic" destruction of body protein may be prevented by large carbohydrate intake, the mechanism of this "toxic" destruction cannot be a direct (poisonous) injury to body cells and proteins.

6. To maintain nitrogen equilibrium in typhoid fever the food must contain 10 to 15 gm. nitrogen in addition to much carbohydrate. Our experiments show no advantage from a further increase of food-protein

We take pleasure in expressing our obligations to Dr. Armstrong, to Miss Goodrich, to Drs. W. M. Kerr, T. S. Kearns, members of the resident staff of the second division of Bellevue Hospital, for many courtesies and assistance during the work; to Mr. M. I. Smith and Dr. G. H. Bentz for assistance in the laboratory, and to Dr. C. L. Dana for the privilege of continuing the work during his service in the hospital.

414 East Twenty-sixth Street—58 West Fifty-fifth Street.

GONOCOCCEMIA

WITH A REPORT OF SIX CASES IN WHICH THE GONOCOCCUS WAS ISOLATED FROM THE BLOOD DURING LIFE *

ERNEST E. IRONS, M.D.

CHICAGO

The occurrence of the gonococcus in the circulating blood in certain forms of gonococcus infection has long been recognized. The demonstration of viable gonococci in the effusions of gonococcus arthritis led to the conclusion that at some time previous to the arthritis gonococci must have been present in the blood. Hewes in 1894 first isolated the gonococcus from the blood in a case of arthritis. The clinical observation that endocardial lesions not infrequently followed local infection by the gonococcus was supplemented by the finding of the organisms in the endocardial vegetations in fatal cases of ulcerative gonococcus endocarditis. Thayer and Blumer[1] in 1896 isolated the gonococcus in pure culture from the blood during life in a case of ulcerative endocarditis, and post-mortem demonstrated the organism in the endocardial vegetations. Faure-Beaulieu[2] in 1906 collected thirty-four cases from the literature in which the gonococcus was isolated from the blood during life. This series included cases of arthritis, endocarditis, and sepsis without local manifestations. Külbs,[3] in a review of the literature of gonococcus endocarditis up to 1907, found records of about 100 cases, in 30 of which the organism was demonstrated post-mortem either microscopically or by culture.

Cases of continued fever in some instances resembling typhoid have frequently been observed in the wake of gonorrhea, and gonococcus sepsis without demonstrable localization has been recognized as a clinical entity. Thayer[4] in 1905 reported a non-fatal case of this kind in which the gonococcus was isolated from the blood. Recently Dieulafoy[5] has reported

---

* From the Memorial Institute for Infectious Diseases and the Presbyterian and Cook County Hospitals.

1. Thayer and Blumer: Johns Hopkins Hosp. Bull., 1896, vii, No. 61.
2. Faure-Beaulieu: Thèse de Paris, 1906.
3. Külbs: Wien. klin. Wchnschr., 1907, xx, 11.
4. Thayer: Am. Jour. Med. Sc., 1905, cxxx, 751.
5. Dieulafoy: Bull. de l'Acad. de méd., 1909, lxi, 594.

a case of gonococcus sepsis with recovery without demonstrable heart lesion in which the gonococcus was isolated repeatedly from the blood.

Hewes,[6] Unger,[7] Oro,[8] and others have isolated the gonococcus from the blood during the course of gonococcus arthritis.

When we consider the prevalence of gonococcus infection, with its attendant complicating involvement of the serous membranes, prominent among which are those of the heart and joints, it becomes evident that the gonococcus is one of the most frequent invaders of the circulating blood.

Chief among the factors which have combined to render the demonstration of the gonococcus in the blood relatively rare, compared with the frequency with which a bacteriemia is demonstrated by culture in typhoid fever and pneumonia, may be mentioned the difficulties in growing the gonococcus, its relatively small numbers in the blood (judging from most of the cases in which it has been demonstrated), its probable sporadic occurrence in the blood from time to time in any given case (e. g., arthritis) and finally our failure to regard cases of metastatic gonococcus lesions as presenting a possibly demonstrable gonococcemia. In many cases of systemic gonococcus infection the diagnosis remains obscure, by reason of the clinical resemblance to other diseases, such as typhoid fever, acute rheumatic fever, malaria, or some of the other forms of sepsis, and it not uncommonly happens that only late in the course of the disease or at the post-mortem table is the true etiology discovered.

It is the purpose of this paper to call attention to certain of the clinical features of gonococcemia, and to the value of blood cultures in the diagnosis, as illustrated by cases in the literature and by six cases which I have observed.

CULTURAL METHODS FOR THE ISOLATION OF THE GONOCOCCUS

The difficulty in growing the gonococcus in the laboratory has been remarked by all who have undertaken a serious study of it. Strains of the gonococcus, apparently vigorous, suddenly die out after two or three generations, despite all precautions. Other cultures may be maintained for long periods of time by repeated transfers on suitable media. Thus I was able to preserve two cultures through 176 generations for a period of two and one-half years. Laitinen[9] recovered the gonococcus from a

6. Hewes: Boston Med. and Surg. Jour., 1894, xxxi, 515.
7. Unger: Deutsch. med. Wchnschr., 1901, xxvii, 894.
8. Oro: Gior. internat. d. sc. med., 1902, p. 291.
9. Laitinén: Zentralb. f. Bakteriol. u. Parasitenk., xxiii, 875.

fluid culture sixty-one days old. It is not uncommon to find living gonococci in fluid cultures two weeks old. There is some difference of opinion as to the virulence of older cultures. Some strains undoubtedly lose their virulence, but in others virulence has been retained to a remarkable degree.

The cultural requirements of the gonococcus are well known and need be given only passing mention. Briefly, they are proper conditions of (1) culture media, (2) temperature, and (3) moisture.

The gonococcus usually grows only on the more highly albuminous media. In the cases reported in this paper the best results were obtained by the use of large tubes or flasks of ascites broth containing 30 to 100 c.c., and of ascites blood-agar plates. The addition of 30 per cent. to 50 per cent. ascites fluid favors the growth of the organism, supplying a highly albuminous medium, and in the case of the blood-agar plates, acting as a diluent for antibodies in the blood which may possibly exert an inhibitive influence on growth. The reaction of the agar and broth before the addition of the ascites fluid was 10 acid to phenolphthalein. Media containing glucose or glycerin, which have been recommended for the cultivation of the gonococcus, were employed at times, but their use gave results no better than those obtained with the usual media.

In making blood-cultures 10 to 20 c.c. of blood were withdrawn with the ordinary aseptic technic from the median vein of the arm and at once distributed among tubes of ascites broth and tubes of melted agar, to which ascites fluid had been added. Plates were poured and the cultures transferred at once to the thermostat.

Growth appeared usually after forty-eight hours as small, grayish, raised, moist colonies. In fluid media the colonies could be seen sometimes at the end of forty-eight hours, though occasionally three or four days were required before the small, round, whitish colonies became visible in the otherwise clear medium.

In maintaining stock strains of the gonococcus transfers were made at first at intervals of two or three days (later seven days), using tubes of blood-agar or ascites-agar. It has been noted by many workers that the older strains of the gonococcus become able to grow on plain agar and other ordinary laboratory media. In certain instances this characteristic appears to be acquired in comparatively young cultures as early as the fifth or sixth generation. In the cases here described, however, the inability to grow on ordinary media was insisted on as one of the criteria for the identification of a culture as gonococcus.

Of scarcely less importance than proper media for the growth of the gonococcus are favorable conditions of moisture and attention to this

point will obviate many failures in its cultivation. The gonococcus is extremely sensitive to the effects of loss of moisture and a freshly prepared medium with moist surface is requisite to good growth. The maintenance of a moist atmosphere in the thermostat is of value, as are also the use of well-fitted Petri dishes, snugly stoppered tubes, and an abundant volume of ascites blood-agar mixture.

Not only should the temperature of the thermostat be kept at as nearly 37 C. as possible, but care must be taken to avoid chilling of fluids or cultures containing the gonococcus in their transfer from the patient to the thermostat. Several workers have recently called attention to the susceptibility of gonococci, in body fluids, to even slight lowering of the temperature. This applies particularly to cultural work during the colder months, where the material must be transported some distance to the laboratory. It goes without saying that in pouring plates the melted agar should always be cooled at least below 40 C., the thermal death-point of the gonococcus being usually estimated at 41 to 42 C.

These points in technic are all more or less elementary, but attention to them is essential to success in the cultivation of the gonococcus. It is the lack of optimum conditions of growth which no doubt has been responsible for the failure to detect the gonococcus in the blood in many cases in which, to judge from clinical manifestations, it was present.

CHARACTERISTICS OF GONOCOCCUS LESIONS

The relatively benign character of the lesions caused by the gonococcus is a matter of general clinical experience. Definite suppuration is relatively rare, considering the frequency of metastatic lesions. The involvement of serous membranes, particularly those of joints, tendon sheaths, bursæ, and the endocardium and pericardium, is a common observation; periarticular and periosteal inflammation is by no means unusual and there is scarcely a tissue of the body which has not been found the site of gonococcus infection.

In spite of its reputed benign character as regards suppuration, the gonococcus more than makes up in the chronicity of its lesions what it lacks in virulence, and is able to live for months and even years in some latent focus, and then, often without apparent exciting cause, to initiate a lesion in some distant portion of the body. Furthermore, the gonococcus not infrequently is accompanied or followed by other pyogenic organisms which hasten the fatal outcome of the pathologic processes already begun.

The port of entry of the gonococcus is usually the genital tract, though general infection with accompanying arthritis has followed gono-

coccus ophthalmia. Metastatic lesions have been seen to follow simple anterior urethritis, and even balanitis, without urethritis (Macaigne and Finet), but as a rule the deeper tissues are involved before general infection occurs. Posterior urethritis (Colombini, Ahlman), epididymitis (Bjelogolowsy, Prochaska), periurethral abscess, and prostatitis in men, Bartholinian abscess, and pyosalpinx in women are the usual antecedent lesions. Ullman[10] in a discussion of gonococcus septicemia has called attention to the frequent involvement of the prostate and in several cases has demonstrated gonococci microscopically and by culture in thrombi from the prostatic and neighboring veins. Krause[11] records the case of a gonorrheic woman who, following child-birth, suffered from bilateral pyosalpinx, arthritis, high fever, with leucocytosis and enlarged spleen. The gonococcus was isolated from the blood. Recovery followed appropriate gynecologic treatment. Gonococcus arthritis following delivery in previously infected cases is occasionally seen.

GONOCOCCUS ARTHRITIS

The clinical picture of gonococcus arthritis is so well known that little need be said concerning it. In an ordinary case, following by a few days or weeks an initial urethritis or the lighting up of an old urethral infection, the joint involvement, with pain, tenderness, swelling and frequent effusion, the occasional involvement sometimes alone, or more often with others, of the sternoclavicular, temporomaxillary, sacroiliac and interspinal joints, the persistence of the lesion in the primarily involved joints, and the associated clinical symptoms, render the diagnosis obvious. An analysis of a large series of carefully observed cases will demonstrate that gonococcus arthritis is almost always polyarticular. Even in the chronic monarticular hydrarthrosis, careful attention to the history will frequently show a multiple initial joint involvement.

Transient arthritis in several joints without pronounced swelling, later persisting in one or more joints, is often seen. A review of the recorded cases of endocarditis and septicemia shows that, in about 80 per cent., arthritis of more or less pronounced degree occurred early in the illness, and often was the first symptom complained of. Likewise arthritis, frequently only transient, may occur later in the course of an endocarditis or septicemia.

The joints of gonococcus arthritis in its more chronic forms may exhibit but little tenderness, even at the onset, and the multiple deforming arthritis of the small as well as the large joints, with relatively little

10. Ullmann: Deutsch. Arch. f. klin. Med., 1901, lxix, 309.
11. Krause: Berl. klin. Wchnschr., 1904, xli, 492.

constitutional disturbance, may resemble to a remarkable degree the symptom complex known as arthritis deformans. Indeed, it has been suggested that the gonococcus is one of the chief members of a rather heterogeneous group of organisms concerned in the causation of arthritis deformans. Be this as it may, one occasionally sees arthritic processes of known gonococcus origin which are almost indistinguishable from those of rheumatoid arthritis.

Bouchard,[12] in a discussion of the etiology and pathology of spondylitis deformans of the type described by Marie, advances evidence to show that in many of these cases there has occurred an antecedent gonorrhea. He recites the case of a man of 48, a sufferer from spondylitis deformans, in whom he was able to find no other causal agent except the gonococcus, which was demonstrated in the prostate thirty-seven years after the initial infection. The evidence advanced, while not absolute, is still very suggestive.

A history of preceding trauma obtained in cases of gonococcus arthritis may be misleading. The occurrence of the arthritis and trauma may be sometimes a coincidence, inasmuch as the arthritis is most often found in certain joints, as the knee or ankle, particularly exposed to injury. More often, however, it is probable that an extremely mild gonococcemia is present, and the trauma produces a *locus minoris resistentiæ*, which allows the development of the organisms in the tissues of the joint, with resulting symptoms. Diggelmann has called attention to the tendency of gonococcus arthritis to localize in the joints affected in an antecedent acute articular rheumatism.

Associated with arthritis, other lesions, as periostitis of the os calcis, malleoli, etc., bursitis and tenosynovitis, are frequent, and may give a clue to the diagnosis in obscure cases.

Examination of the joint fluid is of great importance and many times leads to the correct diagnosis in doubtful cases. The fluid is usually pale yellow, somewhat cloudy, and rapidly coagulates on standing. In hydrarthroses of long duration the fluid is often extremely gelatinous, passing through the aspirating needle with great difficulty. A cytologic study of the centrifuged fluid will show polynuclear leucocytes in considerable number, with large endothelial cells and very few mononuclear leucocytes. The excess of polynuclear cells may be of assistance in certain instances in which the diagnosis lies between gonococcus and tuberculous arthritis. In the early cases it is often possible to demonstrate gonococci, both in the leucocytes and lying free in the fluid, but the diffi-

12. Bouchard, C.: Nature blennorrhagique du rheumatisme vertébral. Ztschr. f. klin. Med., 1907, lxii, 19.

culties of the search become progressively greater with the increase in duration of the arthritis.

The proportion of cases in which the gonococcus can be obtained in cultures from the joint fluid is variously estimated at from 30 per cent. to 70 per cent. The more acute cases give the larger proportion of positive results. Cultural methods will often succeed where microscopic examination has failed to show the gonococcus in joint fluids.

The constitutional symptoms of fever, malaise, etc., in gonococcus arthritis vary greatly in degree from a slight indisposition with fever of 99 to 100 F. to the most severe forms of septic or typhoid-like temperature, with delirium, dry tongue, and rapid pulse. Moreover, the severity of the constitutional symptoms is by no means always proportional to the degree of joint involvement. This observation is easily accounted for when we consider that the arthritis may be merely the most striking incident in the course of a general gonococcemia and that the symptoms are those of general sepsis. Such a case (Case 6) was observed in a young man, the subject of a moderately severe arthritis. Following a few hours of indisposition, his fever, which had previously ranged from 99 to 100 F., suddenly rose with a chill to 103 F., and an extension of the arthritis to the right ankle occurred. Within twelve hours after the rise in temperature blood cultures were made, from which the gonococcus was isolated in pure culture. The organism was isolated also from the effusion in the ankle joint. In the course of a few days the fever subsided, the arthritis improved, and the patient left the hospital in one month, able to return to work. There was no evidence of heart lesion during the illness or convalescence. This case, and others (Oro, Unger), support the contention that the arthritis is but one manifestation of the bacteriemia which is present in the arthritic cases.

Severe toxic symptoms, with high fever, etc., associated with arthritis of the knee, for instance, do not necessarily indicate that suppuration in the joint has occurred. I recently observed a case illustrating this point in a man with arthritis of the knee, from the effusion of which the gonococcus had been isolated. His fever began to rise, and within a few days he became profoundly ill. There was no other demonstrable focus of infection and the surgeon in charge, suspecting purulent arthritis, opened the joint. No pus was found. The fever continued and the joint was again opened, with similar result. After five weeks the fever subsided and the patient made a good recovery without demonstrable heart lesion. The gonococcus was not isolated from the blood, but there can be little doubt that in this case the general symptoms were due to gonococcemia.

GONOCOCCUS ENDOCARDITIS

In addition to the many instances of ulcerative endocarditis of gonococcus origin there is much clinical evidence to indicate that gonococcus infections of the heart valves may heal, with resulting valvular deformities such as are found in the benign endocarditis following articular rheumatism. The appearance of a murmur in a previously normal heart, together with cardiac irritability without other apparent cause, developing during the course of an infection by the gonococcus, and the occurrence of the signs of valvular defects following gonorrhea, in previously normal subjects are points in favor of this view. Withington[13] has recorded a non-fatal case in which the signs of progressive valvular defect and cardiac irritability developed in the course of a gonococcus infection in a previously normal individual, from whose blood the gonococcus was isolated. The evidence presented in this case argues strongly for the healing of gonococcus endocarditis. Similar cases have been cited by Silvestrini, Loeb,[14] Prochaska, and others. In a patient with a gonococcus infection in whom the signs of valvular lesion appear and then subside, without the development of the signs of ulcerative endocarditis, one should, however, be cautious in assuming that the lesion is of the so-called benign type, for the gonococcus, true to its characteristics elsewhere in the body, may persist in the cardiac vegetations and months later give rise to a frankly ulcerative process (See Case 1 of this series, to be referred to later). Then, too, there is always the possibility of a reinfection of the damaged heart valves, either by gonococci which enter the blood from some persistent focus elsewhere in the body or by other secondary pyogenic organisms.

There are approximately 120 cases of gonococcus ulcerative endocarditis on record, in several of which pericarditis has been present. The clinical picture of the gonococcus form does not differ essentially from forms due to streptococcus and pneumococcus, except possibly in the frequency of lesions in the aortic valves. Külbs, in his analysis of 49 well-authenticated cases in 37 men and 12 women, found the following proportion of valvular involvement: Aortic, 28 times; mitral, 8; pulmonic, 6; tricuspid, 1; aortic and mitral, 3; mitral and tricuspid, 1; aortic, tricuspid and mitral, 1; all valves, 1. The course may be rapidly fatal (Case 3) or may extend over months or years (Cases 1 and 2). In type, also, gonococcus endocarditis resembles the other forms, in that in some cases the mechanical valvular defect dominates the picture, in

13. Withington: Boston Med. and Surg. Jour., 1904, cli, 99.
14. Loeb: Deutsch. Arch. f. klin. Med., 1900, lxv, 411.

others the febrile or septic features are the most prominent. Infarcts rarely become suppurative. Petechiæ are apparently less frequently observed than in other forms. They were not observed in Cases 2 and 3 of this series. They were present in large numbers in one of Thayer's cases, but are not mentioned in a number of cases in which the complete histories are given.

GONOCOCCUS SEPTICEMIA

The term "gonococcus septicemia" is here used in a clinical sense to include the group of cases in which the symptoms of sepsis predominate without pronounced arthritis or demonstrable endocarditis. In all three of the groups under discussion gonococcemia, either transient or persistent, is present, and the type of the disease is determined by the lesion which dominates the clinical picture. Faure-Beaulieu, in his review of 34 cases in which the gonococcus was isolated from the blood, found only 3 in which there was no localization in the joints or heart valves. To these may be added one of the cases of Dieulafoy already referred to. These figures, however, by no means represent the relative frequency of the septic type of gonococcus infection.

Padula and others have described a type of remittent fever in the subjects of uncomplicated gonorrhea, with enlarged spleen and other signs of mild general infection. These cases are not unusual in general practice, but the illness is too frequently ascribed to the local lesion or to some assumed but undiscovered focus, rather than to the gonococcemia which a careful blood examination may demonstrate.

Other cases of relatively mild type of septicemia are observed in patients who in months or years past have suffered from an arthritis which has healed or become quiescent. A young man (Case 1) presented the following suggestive sequence of events: Gonorrhea 10 years ago; recurrence eight years ago, with epididymitis and hydrocele; polyarthritis with effusion in the right knee six years ago; recurrence of gonorrhea five years ago, with no urethritis for four years; frequent recurrence of arthritis of knee, which at present is tender, with slight effusion; for five months attacks of irregular fever at intervals of ten days, with occasional chills and general malaise. On admission to the hospital during one of these accessions of fever of five days' duration the case presented several points of difficulty in diagnosis. The continued fever during the early days of observation, together with the presence of several hyperemic maculo-papules on the abdomen, suggested a possible typhoid complicating a previously existing arthritis. The subsequent change in fever curve to that of an irregular type, the absence of later typhoid phenomena, the leucocytosis, the failure of the agglutination reaction, together with

the absence of typhoid bacilli and the presence of gonococci in the blood, determined the diagnosis of gonococcus sepsis. On several occasions a mild arthritis of the smaller joints of the hands occurred. The fever subsided during the two months of hospital observation, but at the time of the patient's discharge there was still an evening rise to 100 F. The general physical condition on leaving the hospital was fairly good, and there was no definite evidence of endocardial lesion. Twenty months later the patient reported that he had had frequent attacks of irregular fever and that he was now suffering from palpitation and dyspnea. The slow ravages of chronic gonococcus infection, with gonococcemia of probably over two years' duration, and a possible chronic ulcerative endocarditis are strikingly illustrated in this case.

Still other cases of gonococcus sepsis run a severe and rapidly fatal course, with high fever and pulse, and delirium. A man (Case 5) addicted to the use of alcohol entered the hospital suffering from pain in many joints of two weeks' duration, fever, and mild delirium. On admission urethritis was not observed, and a provisional diagnosis of acute articular rheumatism with alcoholism was made. The discovery of a slight urethritis, followed by the detection of the gonococcus in the blood, made the diagnosis clear. The fever curve was sustained (See Chart 5) without remissions and gradually rose toward death, which occurred on the twentieth day of the disease. Examination of the heart during life gave no evidence of endocardial lesion. A number of small, slightly raised, reddish maculo-papules which partially faded on pressure, were seen over the abdomen. These resembled petechiæ somewhat more closely than the roseola of typhoid.

Another similar case (Case 4) was that of a woman in whom a provisional diagnosis of articular rheumatism was made. She entered the hospital on the fifth day of her illness, suffering from multiple arthritis involving the ankles, knees and wrists. A purulent arthritis and periarthritis of a finger-joint developed, in the pus of which the gonococcus was found in large numbers. The gonococcus was isolated in pure culture from the pus and from the blood. The fever was of the continued type without remissions (Chart 4), with signs of profound sepsis, and death occurred thirteen days after the first symptoms were noted.

More puzzling at times are the cases in which the clinical picture closely simulates that of typhoid fever. Dieulafoy (1909) recites the case of a man of 23 who had been sick for eight days, with headache, high fever and diarrhea. On the abdomen were a number of red hyperemic papules resembling rose spots, the spleen was enlarged, and the patient presented a typical typhoid appearance. Sweating was profuse.

Agglutination tests with various strains of typhoid and paratyphoid bacilli were repeatedly negative. The gonococcus was isolated from the blood on several occasions, but no typhoid bacilli were found. The gonococcus was found in the sputum also later in the illness. The fever curve was fairly typical of typhoid with defervescence on the fortieth day. Curiously enough, a few days later the patient suffered a second rise in temperature, which ran a typhoid-like course, and now typhoid bacilli were isolated from the blood, and characteristic agglutination phenomena obtained with the serum.

Dieulafoy reports another case of arthritis with demonstrated gonococcemia in which the fever curve was more irregular. In this instance also typhoid fever followed the gonococcemia.

Malaria and pyemia due to other pus organisms may be suggested by the marked oscillations of the fever curve in some cases of gonococcemia. In one of Wynn's cases[15] abscesses over the right hip and in the calves of both legs were observed, in the pus from which gonococci in pure culture were obtained. The gonococcus was isolated from the blood before death. At autopsy, in addition to the multiple abscesses, recent endocardial vegetations were found without definite ulceration. In a second case Wynn observed multiple abscesses over the body, associated with gonococcemia.

OTHER COMPLICATIONS OF GONOCOCCEMIA

Pericardium.—Pericarditis has been noted clinically in a number of cases (usually fatal) of gonococcus septicemia. It is often exudative. Tyree,[16] in a review of the post-mortem reports in cases of gonococcus infection, finds the pericardium involved in 40 per cent., the lesions varying from a slight ecchymoses to serous, fibrinous, hemorrhagic, or purulent exudates.

Lungs and Pleura.—Bressel[17] has reported a case of gonococcus pneumonia, beginning on the fifteenth day of a urethritis. Definite signs of consolidation were present in the lung, and gonococci were found in the expectoration as well as in the blood. Convalescence began on the eighth day of the pneumonia. Dieulafoy saw in his second case bilateral bronchopneumonia in which the gonococci were isolated from the sputum. Although gonococcus pneumonia may occur, by far the larger proportion of pulmonary lesions are due to infarction, or to passive congestion from the increasing valvular defects of the endocarditis with which they are usually associated.

15. Wynn: Lancet, London, 1905, i, 352.
16. Tyree: International Clinics, series 18, ii.
17. Bressel: München. med. Wchnschr., 1903, L, 562.

Pleurisy, often with effusion, is more frequent than pneumonia, and in several instances the gonococcus has been isolated from the cloudy exudate. Prochaska describes a case in which the gonococcus was isolated from the blood and from the pleural effusion.

Signs of fluid were made out in Case 3 of my series, but may have been due to failing heart action. Two days before death this patient suffered severe pain in the chest with cough and bloody expectoration, in all probability marking the occurrence of infarction. Pleural friction without subsequent effusion was noted in Case 1.

Kidneys.—Albuminuria is often remarked in patients suffering from gonococcus infections. Excluding the many cases in which the albuminuria results from an upward extension of the genital infection through the urethra, bladder, ureters and pelvis, there still remain a number of instances in which albuminuria and at times casts have been noted. Renal infarction and passive congestion are often seen in the endocarditic cases. Acute renal insufficiency with anasarca has been observed (Thayer) and post-mortem, cloudy swelling with beginning interstitial changes have been found (Harris and Johnston, Wynn). Ahman noted a persistent albuminuria in a patient convalescent from gonococcemia, and there is considerable clinical evidence in favor of the view that gonococcus infection may give rise to both acute and chronic forms of nephritis.

Spleen.—Splenic enlargement is frequent in gonococcemia either as an acute splenitis such as is seen in other acute infections, or as the result of infarction. In gonococcemia of the typhoid type, the occurrence of splenic tumor should be borne in mind. In 42 cases of demonstrated gonococcemia, including arthritic cases, the spleen is reported enlarged in 15. In a number no record as to this finding appears, and in 4 absence of enlargement was noted.

Skin.—The skin lesions of gonococcemia are of decided interest. The influence of various medicaments, such as the balsams which are held responsible for many of the rashes seen in acute genital infections, can usually be excluded in the cases with general infection. Diffuse erythema, erythema nodosum (Prochaska), erythema multiforme (Barbiani) and extensive purpura (Silvestrini, Achard) have been observed. Petechiæ are occasionally seen in gonococcus endocarditis, though they are apparently less frequent than in cases due to other pyogenic organisms. A generalized petechial eruption is recorded by Thayer.

A hyperemic maculopapular rash resembling very closely the rose-spots of typhoid has been observed in 5 cases (Thayer (2), Dieulafoy, Cases 1 and 5 of this series). In one of Thayer's cases the maculo-

papules were 5 to 6 mm. in diameter, red and surrounded by an area of hyperemia. The rash described by Dieulafoy consisted of hyperemic maculopapules, which were regarded as typical rose-spots until the other findings in the case excluded typhoid fever and determined the diagnosis of gonococcemia. The rash in Case 1 consisted of a few hyperemic maculopapules, resembling rose-spots, and, taken with the continued fever, served to raise the question of the presence of typhoid fever coincident with some other infection. The rash in Case 5 was suggestive of typhoid roseola, but did not entirely disappear on pressure.

Herpes labialis has been observed by Lenhartz and by Thayer, and was present in Cases 1 and 4 of this series.

Profuse sweating has been repeatedly noted, especially in the severe cases of endocarditis and sepsis.

Nervous System.—Organic lesions of the central nervous system have been occasionally observed. Prochaska reports a case of purulent cerebrospinal meningitis in which the gonococcus was recovered in pure culture during life from the blood, and post-mortem from the purulent meningeal exudate, and from pus in one of the seminal vesicles. Thrombosis of the periprostatic veins was also found, but no trace of infection remained in the urethra. There was no lesion found in the heart or lungs. Fürbinger[18] also has reported a fatal case of cerebrospinal meningitis following acute gonorrhea. Cerebral embolism has occurred in gonococcus endocarditis. Delirium and stupor are often observed in the severe toxemias of gonococcus infection. Multiple neuritis and other affections of the peripheral nerves have been described among the complications of gonococcus infections, but their exact etiology, whether toxic or due to actual invasion of the nerve sheaths by the gonococcus, has not been determined in cases in which a gonococcemia has been culturally proven.

Blood.—In addition to the presence of the gonococcus either as a passive transient or oftener as a more or less persistent invader, the blood presents several features of interest in the study of gonococcemia. Polymorphonuclear leucocytosis is almost always pronounced. The relation of the eosinophilic leucocytes described in gonorrheal pus to the leucocytic formula of the blood has been widely discussed. The general consensus of opinion seems to be that in the case of the blood at least eosinophile determinations have no value in diagnosis or prognosis.

Anemia is often a prominent symptom to general gonococcus infection, and gonococcus endocarditis in common with that due to other

18. Fürbinger: Deutsch. med. Wchnschr., 1896, xxii, 424.

organisms may present a rapidly progressive diminution in erythrocytes and hemoglobin.

Studies of the antibodies of the blood serum in gonococcus infection have so far yielded but little information which can be utilized clinically in diagnosis and treatment. Observations on the opsonic index in cases of arthritis and sepsis have in certain instances afforded valuable diagnostic information, but in general the difficulties in technic and interpretation of results, peculiarly pronounced in the case of this organism, relegate the opsonins to a place of subsidiary diagnostic importance. Agglutinins and precipitins have been demonstrated in relatively high dilutions in the immune sera of animals, but these results have not yet been made available for use in clinical diagnosis.

Other Organs and Tissues.—The liver is but rarely involved directly in gonococcemia. Silvestrini (quoted by Faure-Beaulieu) saw an intense icterus in a case of gonococcus infection, in which he isolated the gonococcus from the blood. The icterus appeared on the eighth day of the general infection and persisted for several days. Passive congestion, cloudy swelling and fatty changes are the most frequent postmortem findings.

Ocular lesions, including conjunctivitis, keratitis and iridocyclitis, have been noted, usually in association with other metastatic lesions. Faure-Beaulieu found 6 such ocular complications in 34 cases of gonococcemia.

Mild angina was present in two cases reported by Thayer, and was also found at the onset of illness in Case 1 of this series.

Gonococcus lesions of the cellular tissue, tendons and muscles as a rule do not cause suppuration, but multiple abscesses, both subcutaneous and deep, have been described (Wynn) in which the gonococcus was the only organism present.

Peritonitis, which usually develops by local extension from adjacent structures in the pelvis, may occur as part of a general gonococcemia. Dieulafoy refers to a case studied by Scherrer, in which purulent peritonitis was associated with a pleural effusion. Previous to his illness the patient, a soldier, had suffered from a mild gonorrhea of a few days' duration. On his return from a march he was seized with chills, high fever and headache, followed by diarrhea and moderate dyspnea. The tentative diagnosis of typhoid fever was rendered more probable by the occurrence of sudden abdominal distention, tenderness on pressure and hiccough. On the day following the appearance of the signs of peritonitis the dyspnea became more pronounced and pleural effusion was detected. The patient died on the eighth day. At autopsy, purulent peri-

tonitis, pleurisy with effusion, and recent mitral endocarditis were found, and the gonococcus was isolated from the exudates and from the valvular vegetations. There was no intestinal perforation or visible lesion of typhoid fever.

In severe gonococcemia, emaciation is often a striking feature, due no doubt to the continued toxemia and the coincident anorexia.

Diarrhea has been noted at the onset of several cases of gonococcemia. Glycosuria, probably symptomatic, was noted in Case 3.

DIAGNOSIS

Generalized gonococcus infection in its several clinical forms, such as the arthritic, endocarditic or septicemic, in which a history of preceding genital infection is obtained, may present no special difficulty in diagnosis. It often happens, however, that gonococcus infection is denied, and on examination no signs of urethritis are found. The disappearance of urethritis coincidently with the onset of chill, fever, and other symptoms of general infection has been frequently remarked by clinicians, and is a fact which should be always borne in mind in otherwise suspicious cases. In the same connection, alcoholic excesses have frequently preceded the onset of general gonococcus infection in individuals supposedly cured of an antecedent gonorrhea.

Gonococcus arthritis may simulate very closely acute articular rheumatism. The arthritis may subside rapidly in the joints first involved, thus suggesting the migratory arthritis of rheumatism, the resemblance to which may be further increased by the high irregular fever, occasional mild angina, leucocytosis, and absence of signs of urethritis. From a therapeutic standpoint, the amelioration of symptoms by the salicylates will not always serve to exclude gonococcus arthritis, for in certain instances the analgesic properties of these drugs are pronounced.

In the chronic cases, still greater difficulties may be encountered. Monarticular gonococcus arthritis may resemble tuberculous arthritis. The absence of demonstrable tuberculous foci elsewhere, the history of an old gonorrhea, and of previous, perhaps transitory arthritis or periostitis, the leucocytosis, and the microscopic and cultural examination of the frequent effusions in the joint will assist in the diagnosis. Gonococcal inflammations of the articulations and interspinous ligaments of the vertebræ may be extremely chronic and suggest a persistent lumbago. The resemblance of chronic gonococcus arthritis to arthritis deformans has been referred to by Bouchard and others. Exostoses, particularly those of the os calcis, are frequently seen following gonococcus

infection. Baer[18] has demonstrated the gonococcus in these lesions. The *x*-ray is of service in determining the location and extent of the bone changes.

In the obscure acute cases of gonococcus arthritis, bacteriologic examinations of the exudates are of great value, and blood-cultures will at times assist in diagnosis by demonstrating the associated gonococcemia. In the more chronic arthritis, some information is to be gained by the reaction which follows the subcutaneous injection of a suspension of dead gonococci.[20] A rise in temperature, increase in leucocytosis, and increase in pain and tenderness in the affected joints follows the injection in a large proportion of cases.

Ulcerative endocarditis due to the gonococcus presents no constant features which will distinguish this form from those due to other organisms. Other foci of gonococcus infection and a preceding or coincident arthritis are suggestive, and often serve to render the diagnosis practically certain. Careful and if necessary repeated blood cultures, however, are of the greatest importance in demonstrating the gonococcal nature of the endocarditis.

Gonococcus septicemia presents more difficulties in diagnosis than the other forms of gonococcemia. Especially is this true of the typhoid type, in which the fever may be continued with only slight remissions, and the patient may present the picture of severe toxemia with marked prostration, mental stupor and delirium. Enlargement of the spleen, a rash resembling rose-spots, and the diazo reaction of Ehrlich may add to the difficulty of early diagnosis. The presence of leucocytosis, which is practically constant in gonococcus septicemia, the absence of the agglutination reaction, the complications of arthritis and pleurisy, and the occasional irregularities in the fever cure, will argue against typhoid fever. Herpes labialis is more frequent in gonococcus infections than in typhoid fever. Finally cultures will demonstrate the presence of the gonococcus and the absence of the typhoid bacillus in the circulating blood.

PROGNOSIS

Taking into consideration the frequency with which the gonococcus occurs as a transient invader of the blood in arthritis and other metastatic lesions, it must be admitted that the prognosis of the milder forms of gonococcemia is relatively good so far as prolongation of life is concerned. The more severe cases of septicemia are frequently fatal. Sev-

19. Baer: Surg. Gynec. and Obst., 1906, ii, 168.
20. Irons: Jour. Infect. Dis., 1908, v, 618.

eral instances of recovery from severe gonococcus septicemia without demonstrable endocarditis have already been referred to, but in most of these there are no data given as to the history of the patient in the months and years following the period of observation. In some instances recovery was no doubt permanent, but there is always the possibility that in a certain number of cases the clinical recovery corresponded only to a period of inactivity of the infecting organism or of temporarily increased resistance of the host. A case in point is that of the young man (Case 1) who gave a history of fever and other constitutional symptoms of general infection for five months preceding the finding of the gonococcus in the blood. At this time there were no definite signs of endocarditis. Twenty months later (over two years from the onset of febrile attacks) he still was suffering from periods of fever, associated now with dyspnea and palpitation.

A survey of the autopsies in fatal cases of sepsis and pyemia without symptoms of endocarditis shows that, in a surprisingly large proportion, endocarditis, either vegetative or ulcerative, was found.

It is undoubtedly true that gonococcus endocarditis of the vegetative type may heal, leaving only the symptoms of valvular deformity similar to those following articular rheumatism. Recovery from the ulcerative form has also been reported (Withington, Loeb), but most cases of gonococcus ulcerative endocarditis are fatal, the course varying in time from a few weeks to many months.

CASE 1.—The patient, W. B., male, aged 28, married, clerk, entered Presbyterian Hospital in the service of Dr. Herrick, Sept. 12, 1907.

History.—Five days ago (September 7) the patient noticed a slight chilliness, followed by some fever. The following day the fever was somewhat higher, "the bones ached," the throat felt sore, and in the evening emesis occurred. There was no headache or nose-bleed. September 11 there was pain in the left chest accompanied by dry cough. For five months (since April, 1907) the patient states that he has had attacks similar to the present at intervals of seven to ten days, characterized by afternoon fever and sensations of chilliness. In August, 1907, he had an attack which kept him from work for three days. Six years ago the right knee became painful, with effusion in the joint. At this time the right shoulder also was painful, and there was some fever present. At irregular intervals ever since the pain and swelling in the right knee have recurred. At present the knee is slightly tender but not more so than for the past few months. Eight years ago the right testicle was swollen. This was followed by hydrocele, which recurred two years ago. Gonorrhea ten years ago, with recurrences eight years and five years ago. For the past four years there has been no urethritis observed. Five years ago the patient had a soft chancre. Has had no rash, alopecia or adenopathy. There is no history of typhoid or pneumonia, nor exposure to tuberculosis. No history of alcoholism.

Examination.—The patient is a young man, rather slim, somewhat anemic, musculature flabby. Temperature 103 F., pulse 120, respirations 24. The tongue is moist, with white-coated center. The tonsils are moderately enlarged and hyperemic. Pharynx slightly hyperemic. Hearing is defective in both ears

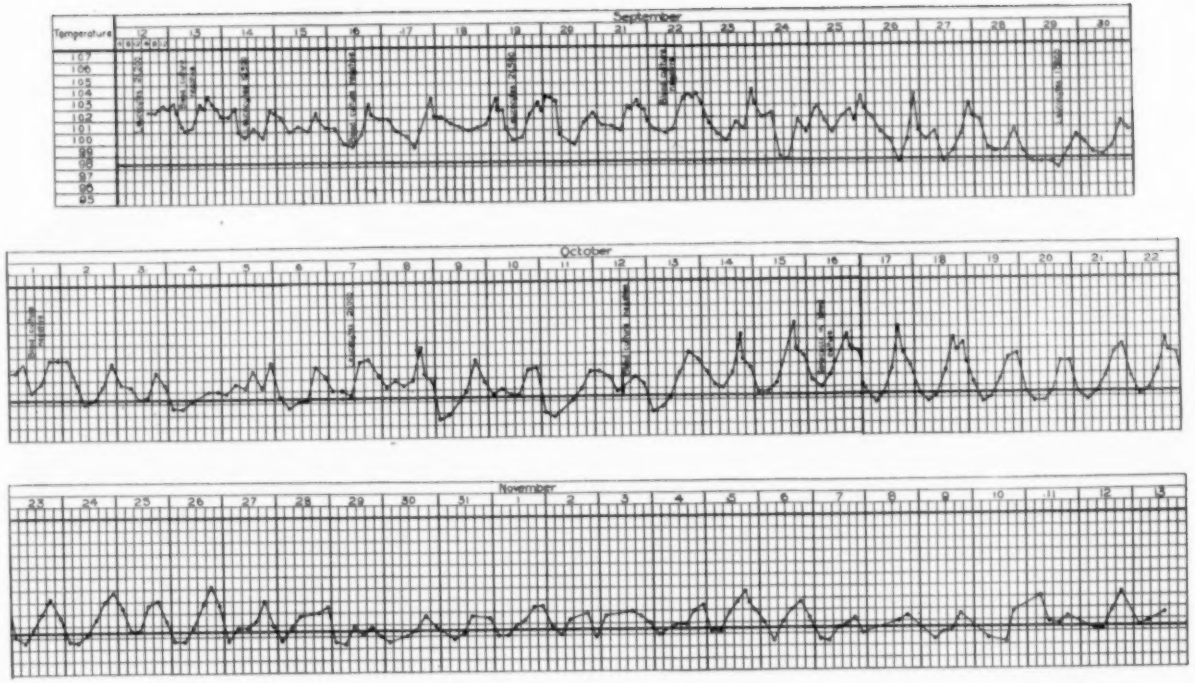


Chart 1.—Temperature, leucocyte counts, and results of blood cultures in Case 1, gonococcus septicemia.

(present since childhood). No cervical adenopathy. Over the left chest in the axillary line there is a faint friction, but otherwise the lungs show no changes. The heart outlines by percussion are normal; the heart tones are pure, no murmurs. The abdomen is normal in contour; there is no tenderness or rigidity. Several reddish maculopapules, which disappear on pressure, are seen on the abdomen. The spleen is not palpable. The liver is not enlarged or tender. A moderate hydrocele is present on the right side. The right knee is slightly swollen, tender, and a small amount of fluid is present in the joint. The pupillary and tendon reflexes are normal.

Urine: Clear, amber, acid, specific gravity 1025. Albumin, a trace; no sugar; few leucocytes, no casts nor blood.

Blood: Reds, 5,160,000; whites, 21,200; hemoglobin, 75 per cent. (Dare). Blood cultures in broth show no growth after four days. Typhoid agglutination reaction negative.

Cultures from the tonsils show a few colonies of the pneumococcus.

Course of Disease.—September 18: Herpes on upper lip. The second interphalangeal joint of the right index finger is slightly swollen and very tender. The temperature (see Chart 1) ranges between 100 F. and 103 F. Pulse 80 to 100. Blood-cultures in bouillon negative.

September 20: Interphalangeal joint of left index-finger acutely tender with slight redness. The swelling in the right knee has subsided.

September 21: Blood-cultures in bouillon flasks negative. Leucocytes, 21,200. No plasmodia of malaria found in the blood. A stained specimen of the urinary sediment after centrifugalization shows a few leucocytes and Gram-negative cocci, but no intracellular organisms. Pain in the left shoulder. Examination of heart shows no murmurs or other signs of lesion. Lungs negative. The fever continues with irregular rises from 100 F. to 103 F., with occasional profuse sweats. The general condition of the patient is about the same as on admission. The mind is clear and alert.

October 16: The general condition of the patient is somewhat better. Temperature averages somewhat lower. The right index-finger remains swollen and tender. The right knee is again tender, and there is evidence of some fluid in the joint. Three toes of right foot are tender, and show slight redness and swelling. Salicylates in the form of aspirin in doses of 40 grains per day have produced no apparent improvement. Potassium iodid in doses of 30 grains per day has been tried, without benefit.

Blood-cultures using ascites bouillon and ascites blood-agar plates after three days show a number of small grayish translucent colonies, identified later as gonococcus. Leucocytes, 27,000; hemoglobin, 65 per cent. (Dare).

Following the isolation of the gonococcus from the blood, the patient was given gonococcus vaccines (stock) in doses of 500 million at intervals of four to five days. In all, five injections were given from October 22 to November 10. The temperature curve which had shown a daily oscillation from normal in the morning to 103 to 104 F. in the evening became gradually lower until the evening temperature was only 100 F. or sometimes lower.

The patient left the hospital November 13. At this time his general condition was better. There was no tenderness or swelling in any of the joints with the exception of the right index-finger, the affected joint of which was stiff and slightly enlarged. A faint systolic murmur was heard at the apex of the heart, and over the third left interspace; the other sounds were normal. The appetite was good. There was still a slight evening rise in temperature.

In July, 1909, in response to a letter, the patient stated that since leaving the hospital in 1907 he has had periods of irregular fever, and that during the past few months he has suffered considerably from palpitation of the heart and some dyspnea.

Summary.—In reviewing the notes of this case, the clinical picture is seen to be that of an exceedingly chronic type of gonococcus infection, from the initial urethritis ten years previously, with relapses or possibly reinfections later, hydrocele and arthritis of recurring type, attacks of irregular fever with occasional chills, and finally a more severe attack of continued fever, arthritis, leucocytosis and demonstrated gonococcemia. Doubtless the gonococcus could have been demonstrated in the blood much earlier had proper media been employed.

During the early days of observation the case presented several points of difficulty in diagnosis in spite of the evident rôle which the gonococcus had played in the previous history. The continued fever, with relatively slight remissions, together with the abdominal maculopapules, some of which at least could not be distinguished from rose-spots, suggested the possibility of typhoid complicating some other infection. Signs of dry pleurisy were noted at the onset.

Acute articular rheumatism, tuberculosis and, later, ulcerative endocarditis of possibly pneumococcus or streptococcus origin were considered.

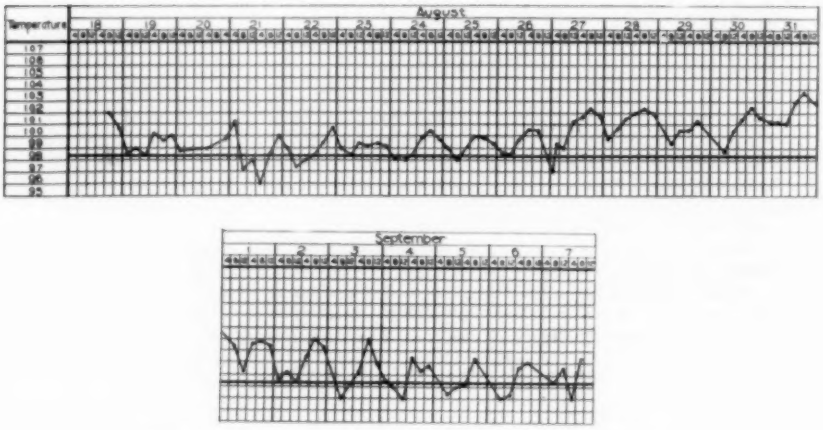


Chart 2.—Temperature in Case 2, gonococcus endocarditis.

During the period of observation in the hospital the patient presented no definite evidence of endocardial lesion. The subsequent history of cardiac difficulty and irregular fever almost two years later suggest very strongly the presence of an ulcerative gonococcus endocarditis which may well have had its origin at the time of hospital observation, or possibly months before.

The value of vaccines in the case is problematical. The gradual fall of temperature and improvement in the joints which followed the use of vaccines without other medication, may have occurred coincidently, and not as a result of the therapy.

Case 2.—The patient, P. D., male, aged 23, single, machinist, entered the Presbyterian Hospital in the service of Dr. Herrick, Aug. 19, 1908. The patient walked into the hospital, suffering from dyspnea, palpitation, gastric disturbance and general weakness.

Past History.—The patient had the usual diseases of childhood; no typhoid or pneumonia. He had gonorrhea two years ago and again eighteen months ago; no arthritis. The first symptom of illness appeared in January, 1908, when the

patient began to feel weak and experienced some shortness of breath and pulsation in the vessels of the neck after slight exertion. About this time he had a severe chill followed by profuse sweating, but went to work next day as usual. On several occasions during January he had severe pain in the region of the heart and thinks he had some fever. In February he had a severe pain beneath the left costal arch, radiating to the back and shoulder. At intervals he has had attacks of anorexia, nausea and vomiting lasting several days at a time. For the past six weeks the patient has been unable to work on account of shortness of breath, palpitation and weakness. Nausea and vomiting have occurred at intervals. Fever has been present at irregular intervals.

Examination.—The patient is a medium-sized, well-built young man; nutrition fairly good, musculature flabby. He lies in bed half-reclining, breathing rapidly and with some difficulty. The lips are of good color; there is marked pulsation in the carotids. Otherwise the head and neck present no abnormalities. A few moist and fine piping râles are heard over the lungs posteriorly. The cardiac impulse is strong and heaving, the apex-beat diffuse, and the area of cardiac dulness increased both to the left and to the right of the sternum. A systolic blowing murmur is heard at the apex transmitted toward the axilla and over the entire precordium. There is also a faint presystolic rumble, heard best at the apex and over the third left interspace. A diastolic murmur is heard over the base, best in the aortic area, but also over the upper precordium, posteriorly in the left scapular region, in the left axilla, and in the vessels of the neck. The radial pulse is quick, strong and collapsing. The quick pulse is easily felt and seen in the finger tips. Capillary pulsation is easily observed over the forehead, lips, etc. The double murmur of Douroziez is heard over both femorals. Blood-pressure systolic right arm 132 mm. Hg., left arm 126 mm. Hg. (Stanton). The spleen is palpable and definitely enlarged. The liver does not extend below the costal arch. The abdomen is otherwise negative. There is no edema of the extremities. The reflexes are normal. The genitalia show no abnormalities. There is no urethral discharge. The prostate is enlarged and slightly tender. On pressure over the prostate a few drops of clear fluid escape from the urethra. Careful search reveals no petechiæ or other skin lesion.

Urine: Clear, amber, acid; specific gravity, 1026. Total in twenty-four hours, 700 c.c. A faint trace of albumin; no sugar; no casts; no blood, a few leucocytes.

Blood: Hemoglobin, 75 per cent.; leucocytes, 9,500. The temperature curve (Chart 2) was irregular, sometimes reaching normal, then rising in a few hours to 102 F.

Course of Disease.—August 22: Blood-cultures made, using blood-agar plates to which 0.5 to 1 c.c. of blood is added. In forty-eight hours four or five grayish moist raised colonies are visible on each plate. This organism was subsequently identified as the gonococcus. From the prostatic fluid, cultures of the colon bacillus, not no gonococci were obtained.

August 26: Gonococcus vaccine (500 million killed organisms) injected subcutaneously in left arm.

August 27: An area 2 cm. in diameter at the site of puncture in left arm is red, swollen and tender (a typical reaction seen when gonococcus vaccine is injected into the subject of a gonococcus infection).

September 2: A second injection of gonococcus vaccine (100 million dead gonococci) prepared from culture obtained from the blood of the patient given.

September 3: For the past two days the patient says he has felt tingling sensations in the left foot and leg. The pronounced pulsation is no longer felt in the felt femoral artery; right femoral shows no change. The temperature of the two feet is apparently the same.

September 4: Tingling sensations continue in the left foot. There is no pulsation in the left posterior tibial, dorsalis pedis, or popliteal arteries. In the left femoral artery near Poupart's ligament, pulsation is faint, and delayed as compared with the opposite side. Patient complains of dyspnea and slight cough. No expectoration.

September 6: Subcutaneous injection of autogenous gonococcus vaccine (100 million). Leucocytes, 10,250; hemoglobin, 80 per cent. (Talquist).

September 11: Subcutaneous injection of autogenous vaccine (100 million).

September 14: Blood: Reds, 4,720,000; whites, 10,550; hemoglobin, 79 per cent. (Dare). Urine: Specific gravity, 1022; acid, clear, yellow. No albumin; no sugar; a few leucocytes in the centrifuged sediment. The temperature of the feet is apparently the same. The pain in the left foot has ceased. Vascular phenomena as before.

September 15: Patient insists on going home.

Death occurred two days later. No autopsy.

Summary.—The history of illness extending over a period of eight months at least, characterized by gradually increasing palpitation, dyspnea, irregular fever and chills, the physical signs of a progressive lesion of the aortic valve, enlarged spleen, and the absence of other foci of suppuration suffice for the diagnosis of ulcerative endocarditis involving the aortic valve. The history of a preceding gonorrhea and the absence of other illness, such as tonsillitis or pneumonia, are

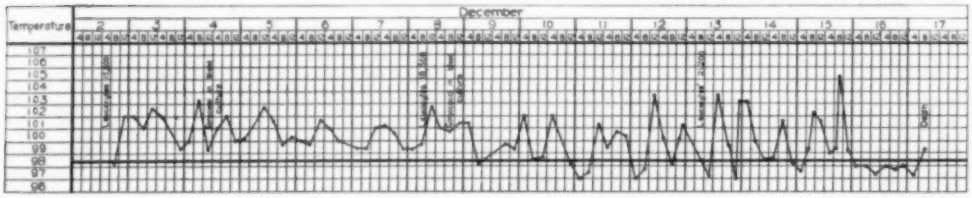


Chart 3.—Temperature and results of blood examination in Case 3, gonococcus endocarditis (acute).

suggestive of the nature of the infection. The isolation of the gonococcus in pure culture from the circulating blood demonstrates the true character of the infection. The partial obstruction of the left iliac artery was probably due to thrombosis. The use of autogenous vaccines in this case was not followed by any observable benefit. The leucocyte counts are lower than those usually found in gonoccus infections.

CASE 3.—The patient, C. O., male, aged 24, married, clerk, was admitted to the Presbyterian Hospital Dec. 2, 1908. The patient consulted Dr. B. W. Sippy (to whom I am indebted for the privilege of observing and reporting the case), suffering from glycosuria, which was believed to account for his general weakness and loss of weight during the previous six weeks. The appetite was poor, polyuria was not pronounced, and the glycosuria had been discovered by the patient's physician in the course of a routine examination. The marked prostration, dyspnea and anemia suggested some cause underlying the glycosuria, and the patient was sent to the hospital for observation. The following history was obtained:

History.—Six weeks ago the patient had a severe chill, followed next day by pain in the shoulders and hips. On the third day there was pain in the right knee. There was no sore throat, cough nor pulmonary difficulty. Antirheumatic treatment was instituted, and two weeks later the patient returned to his work.

During the past four weeks he has suffered very little joint pain, but on several occasions has had chilly sensations. Loss of appetite, general weakness and dyspnea on exertion have been the most prominent symptoms. Three weeks ago he had an attack of severe colicky pain in the abdomen, accompanied by diarrhea for two days. One week before the initial chill the patient contracted gonorrhea. The discharge suddenly ceased at the time of the chill and has not appeared since. There was nothing further of importance in the previous or family history.

Examination.—The patient is a young man, markedly anemic, and weak. The skin is moist. Aside from the anemia, nothing abnormal is noted in the head and neck. There is no herpes. The outlines of the heart by percussion are normal. The apex impulse is felt in the fifth interspace in the mid-clavicular line. A systolic murmur is heard at the apex. The second sound in the pulmonic area is accentuated. The heart action is rapid, but regular. The lungs present no abnormal physical signs. The liver, spleen and kidneys are not palpable. No abdominal tenderness. None of the joints show any tenderness, redness or swelling. No petechiæ are present. Temperature on admission 98.2 F., rising four hours later to 102 (12 p. m.).

Blood: Red cells, 3,728,000; leucocytes, 15,300; hemoglobin, 64 per cent. (Dare). No *Plasmodia malariæ* found.

Urine: Pale yellow, acid, specific gravity 1036, 1700 c.c. in twenty-hour hours. No albumin; sugar 4.6 per cent. (titration)=78 grams in twenty-four hours. Trace of acetone. No diacetic acid. A few leucocytes are present in the centrifuged specimen; no casts or red cells. Agglutination test for typhoid entirely negative in one hour at dilution 1 to 40.

Blood cultures in bouillon show no growth after four days.

Course of Disease.—December 4: Tenderness over left hypothenar eminence. No redness or swelling. The temperature is irregular, ranging from 99 F. to 103 F. (Chart 3). Severe chill and sweat last night. Urine: 1,000 c.c. in twenty-four hours; specific gravity, 1020; sugar, 1.6 per cent. = 16 grams in twenty-four hours. Blood-cultures on ascites blood-agar plates after forty-eight hours show a few small grayish colonies, which morphologically, on staining, and by cultural methods later are proved to be typical gonococcus.

December 8: Dull pain in right shoulder, lasting one hour. No swelling. The spleen is palpable to-day for the first time. The systolic murmur at the apex is heard more plainly, transmitted to the left as far as the axilla. No diastolic murmur is heard. Lungs negative. Urine: 900 c.c. in twenty-four hours; specific gravity, 1022. Sugar, 1.6 per cent. = 14.4 grams in twenty-four hours. Blood: leucocytes, 18,500; hemoglobin, 60 per cent. (Dare). Blood-cultures again show the gonococcus in small numbers (2 to 3 colonies per cubic centimeter of blood).

December 11: Chill to-day and yesterday.

December 12: Vaccine (100 million) prepared from organism isolated from the blood, given hypodermically. Tongue dry and furrowed.

December 13: Signs of small amount of fluid in left chest. The patient is failing rapidly. Dyspnea increasing. Temperature septic in type. Leucocytes, 21,200; hemoglobin, 58 per cent. (Dare). Urine (760 c.c. in twenty-four hours) shows small amount of sugar.

December 16: Severe pain in chest, with cough, and bloody expectoration. Patient unconscious. Pulse rapid (120 per minute), weak and irregular.

December 18: Death. No autopsy.

Summary.—One week after the onset of gonorrhea a young man suffers a severe chill, followed by pain in several joints. The joint symptoms subside, but the chilly sensations and fever recur irregularly, with gradually increasing weakness, dyspnea and loss of weight. Glycosuria without polyphagia or marked polyuria is found, and the patient is brought to the consultant. The history,

weakness, fever, chills and anemia suggest a septic process, and the gonococcus is isolated from the blood. The gradually changing endocardial murmur, together with other signs of cardiac involvement, leave but little doubt that acute ulcerative endocarditis is also present.

CASE 4.—The patient, M. R., aged 37, widow, cook, was admitted to Cook County Hospital Feb. 8, 1909. Diagnosis on admission, acute rheumatic fever.[21]

History.—Five days ago the patient was awakened by pain in the ankles. Within a few hours the knees and wrists became swollen and painful. The joint trouble has become gradually worse, associated with fever, malaise and slight dyspnea. No sore throat. There was no history of any previous severe illness; no rheumatism. The patient has had four children; no miscarriages. For some months the patient has suffered from a profuse greenish-yellow vaginal discharge. Uses alcohol to excess, chiefly in the form of beer.

Examination.—The patient is a well-nourished white woman; of fair mentality; restless, movements tremulous, suggestive of alcoholism. Venules of cheeks and nose are prominent. The right pupil is slightly larger than the left, but both react normally to light and accommodation. Herpes is present on the lips. No cyanosis. Tongue tremulous, dry, with raised red central portion. The glands

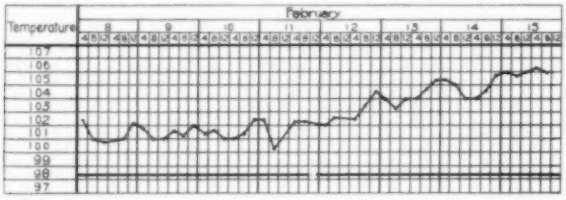


Chart 4.—Temperature in Case 4, gonococcus sepsis with purulent arthritis.

of the neck are not enlarged, nor is there any rigidity of the neck. A few moist râles are heard over the bases of both lungs posteriorly, but otherwise nothing of note is made out. The heart, as outlined by percussion, is apparently normal in size. A faint systolic murmur is heard over the second and third interspaces to the left of the sternum. Otherwise the heart tones are normal. No arrhythmia. The abdominal wall is thick, but there is no rigidity or tenderness. The liver extends 3 centimeters below the costal arch. The spleen is not palpable. A vaginal examination shows a profuse greenish-yellow discharge. There is some atresia of the vagina just below the level of the cervix, but there is no tenderness or palpable tumor mass. A rectal examination shows nothing abnormal. There are no enlarged glands or hemorrhoids. The ankles, right knee and wrists are swollen and tender, as are also the proximal and distal phalangeal joints of the right index-finger. The patellar reflex is rather sharp. No Babinski. The urine is cloudy, specific gravity 1015, acid, contains a trace of albumin; no sugar. Microscopically, pus cells but no casts. Leucocytes, 40,000 per cm. Examination of the vaginal discharge shows many intracellular diplococci.

Course of Disease.—February 12: Blood-cultures made in plain bouillon showed no growth after four days.

February 13: The distal phalangeal joint of the right index-finger is red, swollen and tender. The joint is incised and several cubic centimeters of thick fibrino-purulent fluid escape. Cover glass preparations of the pus show many

21. I am indebted to Dr. Lounsbury, under whose immediate care this patient was, for his notes on the case.

Gram-negative diplococci, both intracellular and extracellular. Cultures on plain agar show no growth after four days. Cultures on human blood-agar show a few colonies after two days, identified later as gonococcus.

February 14: Slight rigidity of the neck. Lumbar puncture made and 13 c.c. of clear fluid under normal pressure withdrawn. Microscopic examination of the centrifuged fluid shows no abnormal cells, and no micro-organisms. The purulent discharge from finger-joint opened yesterday continues. The infection involves the periarticular structure as well as the joint proper. Many intracellular diplococci present in the pus. The arthritis of the ankles and knee has subsided almost entirely. There is distinct crepitus but no swelling or redness in both wrist-joints.

February 15: Patient is decidedly worse; delirious, with gradually rising temperature (Chart 4). Blood-cultures (ascites blood-agar and ascites bouillon) made. The gonococcus was isolated in pure culture from these cultures.

Death occurred February 16, thirteen days after the onset. Autopsy refused.

Summary.—A woman, 37 years of age, an alcoholic, who for some time has suffered from a genital gonococcus infection, is taken suddenly ill with multiple arthritis, fever and symptoms of severe infection, clinically not unlike acute articular rheumatism. Aside from a faint systolic murmur (possibly hemic) there is no definite evidence of endocarditis or pericarditis. The fever from the fifth day (entrance to the hospital) ranges between 101 F. and 103 F., later gradually rising to 106 F. at death. A leucocytosis of 40,000 is present. The gonococcus is isolated in pure culture from a purulent arthritis and periarthritis of the finger, and from the blood during life.

CASE 5.—The patient, P. G., male, aged 39, single, laborer. Entered Cook County Hospital Feb. 12, 1909, suffering from fever, pain and swelling in many joints and a mild delirium. On admission a diagnosis of acute rheumatic fever was made.

History.—At the onset of illness two weeks previously, the patient had first noticed pain in several joints accompanied by fever and malaise. His condition had gradually become worse until entrance to the hospital. He had suffered from no other serious illness; had used alcohol to excess, but had not been drinking for several weeks previous to the onset of the present trouble. Further history could not be obtained on account of the confused mental state of the patient.

Examination.—The patient is a well-developed, well-nourished white man; talks irrationally and is very restless. There is a yellowish purulent discharge from the left eye. The lips are dry and tremulous, teeth bad, tongue dry and covered with a thick gray coating. The lungs show nothing abnormal. The heart dulness is normal, the apex beat somewhat diffuse and cannot be definitely localized. The heart sounds are pure, no murmurs. Pulse rapid, low tension; vessel wall soft and pliable. Spleen and liver not palpable. No abdominal tenderness. Over the abdomen and lower portion of the chest there are a number of small reddish areas about 2 to 3 mm. in diameter which fade only partially on pressure. A slight purulent urethritis is present. The right knee and ankle are reddened, swollen and somewhat tender. Signs of fluid in the knee-joint. Examination otherwise negative. Microscopic examination of the urethral discharge shows intracellular Gram-negative diplococci typical of the gonococcus in appearance. Examination of the discharge from the eye shows diplococci, with very few leucocytes. The fluid aspirated from the knee joint is yellow, turbid and contains many leucocytes and a few cocci. Cultures from the fluid gave no growth, although care was taken to provide conditions of media and temperature favorable to the gonococcus. Leucocytes, 22,150 per cm. Examination of the urine shows a trace of albumin and a number of pus cells. The temperature (Chart 5) was usually about 103 F. with occasional remissions, never falling below 101 F.

There were no definite chills, but some sweating. The general appearance of the patient was that of moderately severe sepsis. The associated urethritis and arthritis suggested the possibility of a general infection by the gonococcus.

Course of Disease.—Blood-cultures taken on February 15 showed the gonococcus in pure culture (2 to 3 colonies per c.c. of blood). Death occurred February 16. No autopsy allowed.

Summary.—A man 39 years of age, alcoholic, the subject of chronic gonococcus urethritis, suddenly suffers from multiple arthritis, fever and symptoms of severe infection. Careful and repeated examinations of the heart show no definite evidence of endocarditis. Over the abdomen and lower chest are a number of small slightly raised reddish maculopapules which partially fade on pressure. There is a leucocytosis of 21,000. The gonococcus is isolated from the blood in numbers of 2 to 3 colonies per cubic centimeter of blood. The fever curve is sustained, with only slight remissions. The pulse in the third week of the illness is rapid. Aside from the laboratory findings and the arthritis of the knee, the clinical course, appearance of the patient, rash and temperature curve are somewhat suggestive of typhoid fever.

CASE 6.—The patient, J. McN., male, aged 22, single, laborer, was admitted to Cook County Hospital Nov. 23, 1907. Diagnosis on admission, chronic gonorrhea and gonococcus arthritis.

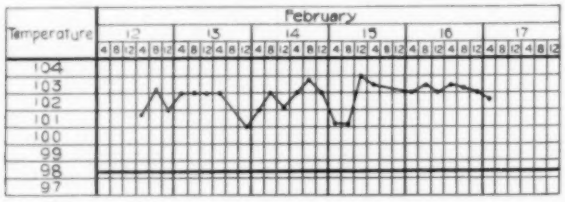


Chart 5.—Temperature in Case 5, multiple gonococcus arthritis, with fatal sepsis.

History.—Four years ago the patient contracted gonorrhea from which he recovered in two months without complications; suffered from a recurrence of urethritis two years ago without arthritis. In August, 1907, a third attack of urethritis was followed in one week by a mild arthritis involving both ankles, knees, wrists and several joints of the cervical spine in rapid succession. The arthritis improved rapidly and the patient returned to work in a few days. A week before admission the arthritis recurred in the cervical spine, left ankle and in both knees and wrists. The heels also had become very tender.

Examination.—The patient is a well-nourished, well-developed young man. Aside from the pain of the affected joints, he does not appear very sick. A careful physical examination reveals nothing of note except the multiple arthritis, purulent urethritis, and a somewhat enlarged tender prostate. The heart is normal in size and the tones are normal. Several of the small joints in the hands and fingers are tender, swollen and slightly reddened. The left knee is tender, with considerable swelling, due both to periarticular infiltration and to a moderate joint effusion. Both ankles are slightly swollen and tender. There is also involvement to a less degree of the lower thoracic spine, and the dorsum of the right foot.

Course of Disease.—Shortly after admission to the hospital the patient suffered from a sudden exacerbation of symptoms. The fever which had previously

reached 100 to 100.5 F. in the morning, rose to 101 and 102 F. The right ankle became more acutely swollen, red and excessively tender; signs of fluid were found. During this exacerbation, blood cultures were made, and the gonococcus isolated in pure culture. No other organisms were found. Cultures from the fluid aspirated from the ankle showed colonies of typical gonococci. The patient remained in the hospital for one month, during which time he improved steadily, and at the time of his discharge the affected joints were practically normal. There were no contractures. Repeated examinations of the heart revealed no signs of endocardial lesion, either during the acute illness or during convalescence.

Summary.—During an exacerbation in the course of gonococcus arthritis in a young man, the gonococcus is isolated from the blood and from the joint fluid in pure culture. There is no clinical evidence during the entire course of the illness of any endocardial lesion.

103 State Street.

TUBERCLE BACILLI IN THE BLOOD

WILBUR A. SAWYER, M.D.
BERKELEY, CAL.

In February, 1909, Rosenberger[1] published his announcement of the finding of tubercle bacilli in the blood of every one of 125 tuberculous patients examined. Previous to that time the prevailing opinion had been that only occasionally in cases of so-called localized tuberculosis[2] did bacilli escape into the blood-stream. It had been supposed that in the miliary form alone was the number of organisms sufficient to give any promise of detection, and that even in these cases the search was apt to be futile. The description by Landouzy[3] of typho-bacillose, a stage of tuberculosis which precedes the formation of localized lesions and which is supposed by him to be a septicemia, had added interest to this subject.

After unsuccessful attempts to confirm Rosenberger's findings in a search of the blood of human beings, I undertook, in conjunction with C. M. Haring, D.V.M., Assistant Professor of Veterinary Science in the University of California, the systematic examination of the blood of tuberculous cattle. The work was done under the Department of Agriculture of the University of California. The investigation has a bearing on meat-inspection, for the blood-containing muscle of cattle with "localized" tuberculosis is now considered to be fit for food and is passed by the government inspectors.

Since this work was begun various reports have appeared, of which some confirm Rosenberger's work while some radically differ from it. Tubercle bacilli have frequently been found in the blood by Forsyth[4] and by Petty and Mendenhall.[5] Rosenberger has reported subsequent positive blood-findings, bringing his total to 300 cases, and has concluded that tubercle bacilli may exist free in the blood of even apparently healthy

1. Rosenberger, R. C.: The Presence of Tubercle Bacilli in the Circulating Blood in Tuberculosis. Am. Jour. Med. Sc., 1909, cxxxvii, 267.

2. Pearce, R. M.: Osler's Modern Medicine, 1907, ii, 657.

3. Landouzy, L.: Tr. Sixth Internat. Cong. on Tuberculosis, 1908, i, part 2, p. 581.

4. Forsyth, C. E. P.: Occurrence of Tubercle Bacilli in the Blood in Tuberculosis. Brit. Med. Jour., April 24, 1909.

5. Petty, O. H., and Mendenhall, A. M.: Tubercle Bacilli in the Blood. Jour. Am. Med. Assn., 1909, liii, 867.

individuals.[6] Failures to find the bacilli have been reported by Ravenel and Smith,[7] Burnham and Lyons,[8] and Dailey.[9] Schroeder and Cotton[10] have announced negative results in their search in the blood of cattle.

An isolated herd of 51 cattle at the University Farm at Davis, Cal., was available for study. In the herd were 42 3-year-old steers and cows. Of these, 22 had been twice inoculated intravenously, when young calves, with attenuated cultures of tubercle bacilli. Of the 42 animals, 12 (3 of the inoculated animals and 9 of the others) gave decided tuberculin reactions. These were selected to form Group B of this investigation. With the young stock were 9 old tuberculous cows which had been added to the herd to test the susceptibility of the others to tuberculosis. These old animals, most of them in advanced stages of the disease, constituted Group A.

The method of examination was essentially taken from Rosenberger. The search of the sediment from laked and centrifugalized blood was added for control and comparison. All glassware (test-tubes, pipettes, syringes, centrifuge tubes, slides, cover-slips, jars) were cleaned with hot washing-powder solution and then subjected for half an hour or more to concentrated nitric acid. The needles were cleaned with soap and water, syringed out in concentrated caustic soda solution, and finally boiled for ten minutes in the latter. The distilled water and the citrate-chlorid solution were examined microscopically and found to be free from organisms. (Attention has recently been called by Brem[11] to the liability of distilled water to contamination with acid-fast bacilli.) Test-tubes each containing 5 c.c. of 2 per cent. sodium citrate and 0.6 per cent. sodium chlorid solution were covered with larger test-tubes, inverted, instead of being closed with the usual cotton plugs. Tubes containing the syringes, needles and solution were placed in a covered jar, sterilized, and carried unopened to the field. The animal to be bled was thrown, and its neck was shaved and scrubbed. Through a needle introduced into the jugular

6. Rosenberger, R. C.: Presence of the Tubercle Bacillus in the Circulating Blood. New York Med. Jour., 1909, lxxxix, 1250.

7. Ravenel, M. P., and Smith, K. W.: Detection of Tubercle Bacilli in the Blood. Proc. State Med. Soc. of Wisconsin, abst. in Jour. Am. Med. Assn., 1909, liii, 649.

8. Burnham, M. P.: Tuberculosis—A Bacteriemia. Jour. Am. Med. Assn., 1909, liii, 731.

9. Dailey, M. A.: The Presence of Tubercle Bacilli in the Blood in Tuberculosis. Boston Med. and Surg. Jour., 1909, clxi, 318.

10. Schroeder, E. C., and Cotton, W. E.: Tests Concerning Tubercle Bacilli in the Circulating Blood. The Archives Int. Med., 1909, iv, 133.

11. Brem, W. V.: Investigation of Blood for Tubercle Bacilli; Contamination of Distilled Water with Acid-fast Organisms a Source of Error. Jour. Am. Med. Assn., 1909, liii, 909.

vein 5 c.c. of blood were withdrawn, added to 5 c.c. of the citrate-chlorid solution, and shaken. Then 5 c.c. more of blood were withdrawn and added to another tube of solution, in order that more sediment might be obtained for inoculation into a guinea-pig. In this way the probability of infection was supposed to be increased. The tubes of blood-mixture were placed in the refrigerator from twenty-four to forty-eight hours. Then five preparations were made from one of the two tubes. Two smears were made from the uppermost part of the sediment and two from the bottom. These were dried and fixed on a copper plate with moderate heat. They were laked in distilled water for from fifteen minutes to three hours, and then stained with carbol-fuchsin (for two minutes steaming or one or two hours cold). One of the specimens from the top and one from the bottom were decolorized for twenty minutes with 1 per cent. rosolic acid in absolute alcohol. The other two specimens were decolorized with either 30 per cent. nitric acid or 20 per cent. sulphuric acid, followed by 95 per cent. alcohol. Methylene blue was used as counterstain.

The tube from which a small part of the sediment had been taken for smears was shaken and 5 c.c. of the mixture (almost 2.5 c.c. of blood) was added to 10 c.c. of distilled water in a centrifuge tube. Laking was complete. Centrifugalizing for thirty minutes brought down a small bit of tenacious reddish white sediment, which was teased out on a cover-slip, dried, and fixed over a copper-plate, stained with carbol-fuchsin, decolorized with rosolic acid solution, and counter-stained with methylene blue. Each of the five specimens was searched at least thirty minutes. When the remaining blood-mixture in the tube had again settled, the sediment from both tubes was injected intraperitoneally into a guinea-pig, which was then placed alone in a cage. The amount of sediment received by the guinea-pig varied from 0.5 to 5.0 c.c. These animals had been previously used in standardizing diphtheria antitoxin. One of the guinea-pigs died a few hours after inoculation, but was replaced after a later bleeding of the animal which had furnished the fatal blood. The earliest of the examinations deviated from the method just described in unimportant details.

Each of the old cows in Group A was bled three times between March 5, 1909, and July 1, 1909, and the blood studied. The blood-sediment of one bleeding from each animal was injected intraperitoneally into a guinea-pig, which, in the case of all but one of the cows, later received the sediment from another bleeding from the same animal. None of the blood-preparations revealed any acid-fast bacilli. Each of the nine guinea-pigs was killed between ten and one-half and eleven and one-half

weeks after its first inoculation. The second inoculation received by eight of them had occurred between eight and one-half and ten and one-half weeks prior to autopsy. The animals were fat, and not one of them showed any macroscopic lesions suggesting tuberculosis.

Each of the 12 young animals of Group B was bled once. The blood-preparations were free from acid-fast bacilli. The blood sediment from each animal, except Steer 51, was inoculated intraperitoneally into a guinea-pig. These 11 guinea-pigs remained in good health until they were killed, ten or eleven weeks after inoculation. No macroscopic tuberculous lesions were found at autopsy. Positive results were scarcely to be expected after the work of Schroeder and Cotton,[10] who injected 88 guinea-pigs with the blood of 42 tuberculous cattle without producing tuberculosis.

From the material from 39 bleedings of the 21 cattle 167 preparations were made and searched 110.9 hours; 133 of the slides, made from gravity sediments, were studied 88.9 hours. From the laked and centrifugalized blood 34 slides were prepared and searched for 22 hours. These examinations failed to reveal any tubercle bacilli.

In order to secure evidence as to whether the failure of guinea-pigs to contract tuberculosis, when inoculated with the blood of tuberculous cattle, was due to protection by the blood injected, the following experiment was performed: Each of three guinea-pigs of about equal weight was injected intraperitoneally with mixtures containing 0.2 c.c. of pus from an axillary abscess of Cow 3 of Group A. This pus contained so few tubercle bacilli that twenty to thirty minutes' search was necessary to find any. One of the guinea-pigs (No. 23) received the pus thoroughly mixed with 5 c.c. of fresh blood-citrate mixture from Cow 3, the source of the pus. Another (No. 25) received the sediment (1.2 c.c.) from a similar mixture of pus and blood. The third (No. 24) received the pus in 5 c.c. of the citrate-chlorid solution. Ten weeks later guinea-pig No. 23 died and the other two were killed. Autopsy showed all three to be emaciated and to be about equally and very generally tuberculous. Apparently no appreciable effect on the presence or severity of infection had been exerted by the blood.

In order to make a study of the methods of detecting tubercle bacilli in the blood, it was attempted to produce artificially the tuberculous bacteriemia which we had failed to find. A cow suffering from advanced tuberculosis (No. 7 of Group A) and a plump 3-year-old steer (No. 18 of the normal animals) were selected for experiment. The cow had a submaxillary abscess from which tuberculous pus and a calcareous gland had been taken. The steer had been twice inoculated when a calf with

attenuated cultures of tubercle bacilli. There was no reaction to the tuberculin test. The animals received in their jugular veins quantities proportional to their weights of a suspension of live bovine tubercle bacilli in normal salt solution. No. 7 received 200 c.c. and No. 18, 250 c.c. The bacilli had been washed, dried, ground dry for ten minutes in a revolving Erlenmeyer flask containing glass balls, and had been rotated for several hours more after the addition of normal salt solution. About 200 mg. of tubercle bacilli were contained in 250 c.c. Smears of the suspension mixed with blood permitted the rough estimate to be made that there were many more free bacilli, and as many clumps, in the suspension injected into No. 18 as there were white corpuscles in the entire circulating blood of the animal. Inasmuch as many corpuscles had been found in almost every field of most of the blood-preparations of this investigation, it was expected that many bacteria would be found in each field of the slides of the steer's blood. No. 18 was bled from the jugular vein, which had not received the inoculation, thirty minutes, five hours, eleven hours, twenty-five hours, forty-six hours, and ten days after inoculation. The routine microscopic blood examination failed to reveal any tubercle bacilli.

Part of a mixture of the blood sediments of the first five bleedings was inoculated intraperitoneally into a guinea-pig, which was allowed to live eleven weeks. Another guinea-pig received the sediment of the sixth and last bleeding and was killed at the end of ten weeks. At autopsy both animals appeared to be entirely normal.

The steer's temperature rose rapidly to 105.5 after inoculation, but fell to normal the next morning. After a few days the temperature began to rise again, and four weeks after inoculation the animal died. Autopsy, performed twenty-four hours after death, showed the lungs to be crowded with miliary tubercles. The spleen contained on the average one miliary tubercle in each square centimeter of its surface. The kidneys contained a few miliary tubercles and the liver none. The mediastinal, inguinal, pelvic, and crural lymph-nodes were enlarged and soft. In the heart were a clot and some red turbid serum. The centrifugalized sediment of this serum showed many coarse bacilli and one group of three tubercle bacilli.

Cow 7 was bled one hour, five hours, eleven hours, twenty-five hours, forty-six hours and fourteen days after inoculation, and the blood was examined. One short structure resembling a tubercle bacillus was found in a smear from the top layer of the sediment drawn eleven hours after inoculation. This slide had been decolorized by the rosolic acid solution. All the other slides were unquestionably negative.

A guinea-pig which received part of a mixture of the sediment from the first five of the six bleedings was killed eleven weeks after inoculation and found to be normal.

The cow's temperature rose immediately after inoculation to 107.5, and in a few hours fell almost to normal. Then the temperature rose gradually to 107.8 and subsided almost to normal. The curve of this last rise and fall suggested the course of a severe tuberculin reaction. No corresponding rise and fall had occurred in the temperature of Steer 18. The cow died nine weeks after inoculation. Autopsy showed extensive chronic lesions and no acute miliary tuberculosis. The right submaxillary, bronchial, anterior mediastinal, portal and mesenteric lymph-nodes were found calcified. The left mediastinal and parotid lymph-nodes were caseous. The left submaxillary lymph-nodes had broken down and had formed a large abscess. Both lungs were extensively involved with old lesions, some connecting with the bronchi. The spleen showed a calcified nodule 2 cm. in diameter. The liver and kidneys were normal.

A third time we introduced tubercle bacilli into the circulation of the cattle and attempted to recover them from their blood. Cow 3 of Group A had advanced tuberculosis. Tubercle bacilli had been found in the pus of a large axillary abscess. The animal was put deeply under the influence of chloral and its right carotid artery was exposed. Fifteen c.c. of suspension of 180 mg. of live bovine tubercle bacilli, which had been washed, dried and ground in a revolving flask for one hour before the addition of normal salt solution, was introduced through a needle into the artery. Blood was withdrawn from the jugular vein of the same side, but from a point distant from the operation wound, twenty-five minutes, one and one-half hours, two days, and six days after the inoculation. The blood drawn twenty-five minutes after the introduction of the organisms showed tubercle bacilli as follows:

A search of seventy minutes in the specimen from the centrifugalized and laked blood showed 5 clumps, one group of 4, one group of 2, and one single bacillus.

A search of fifty-five minutes in the first preparation from the top layer (decolorized by rosolic solution) showed two clumps.

A search of sixty minutes in the second preparation from the top layer (decolorized by nitric acid) showed one clump.

Both smears from the bottom of the sediment (one decolorized by rosolic and one by nitric acid) showed no bacilli after sixty-six and seventy-two minutes' search.

No tubercle bacilli were found in specimens from the bleedings made from one and one-half hours to six days after inoculation.

Half of a mixture of the sediments drawn twenty-five minutes and an hour and a half after inoculation was inoculated intraperitoneally into a guinea-pig. Ten and one-half weeks later the guinea-pig was killed. Three tubercles 2 mm. in diameter were found in the spleen. No other lesions were discovered.

A guinea-pig was inoculated intraperitoneally with the combined sediments of the blood specimens drawn two and six days after inoculation. The animal died six weeks after receiving the blood. Autopsy showed the presence of three full-term fetuses, but no lesions of tuberculosis. The results of the guinea-pig inoculation in this case confirmed the microscopic findings. The natural conclusion would be that the abundant tubercle bacilli had been rapidly filtered from the blood.

The temperature of Cow 3 dropped for two hours after inoculation and then rose rapidly to 106. The temperature soon fell slightly and then slowly developed a marked daily variation. This animal had been running an irregular elevated temperature before the experiment. Death resulted five weeks after inoculation from hemorrhage from a ruptured aneurism at the point of inoculation in the carotid. Autopsy showed many hard tubercles averaging 0.5 cm. in diameter scattered throughout both lungs. One small tubercle was seen in the right kidney and one in the tissues near the aneurism. The mediastinal lymph-nodes were calcareous and the post-pharyngeal nodes were purulent. Most of the lesions appeared to have been of long duration, and autopsy gave no evidence of acute miliary tuberculosis.

The experiments just described show that artificially introduced tubercle bacilli are rapidly removed from the circulation of healthy and of tuberculous cattle. That the capillaries of the lungs are more efficient as filters than the capillaries of the peripheral circulation is suggested by the almost complete, if not entire, absence of tubercle bacilli from blood which had necessarily passed through the pulmonary circulation, and by the presence of bacilli in blood which needed to go only from a peripheral artery to the corresponding peripheral vein. Possibly this quality of the lung capillaries may be one of the causes of the great frequency of pulmonary involvement when tubercle bacilli have entered the body at points distant from the lungs.

It will be noticed that inoculation produced in a healthy young steer a rapid and fatal miliary tuberculosis, while in Cows 3 and 7 not more than an aggravation of the existing extensive chronic tuberculosis was brought about. It would appear that long-standing chronic tuberculosis produced a much higher power of resistance against newly introduced infection than did the intravenous injection of attenuated cultures.

For information regarding the relative value of the methods used in detecting tubercle bacilli each of two tubes of blood-mixture was inoculated with one drop of suspension of tubercle bacilli. The tubes were thoroughly shaken and contents allowed to settle. Search of the usual number of preparations from each tube gave results consistent with those obtained in the positive specimen of blood which had been experimentally inoculated within the artery of Cow 3. In that blood the figures already given showed that the one preparation from the concentrated sediment of the laked and centrifugalized blood showed more bacilli than did all four of the slides from the unlaked gravity sediment, and that the specimens from the top layers of the latter contained bacilli, while smears from the bottom contained none. Each of the specimens from the two inoculated tubes of blood was studied thirty minutes and the following results were obtained:

One preparation from each laked and centrifugalized sediment showed:

First specimen: 21 masses of tubercle bacilli.
Second specimen: 21 large clumps, 3 small clumps, and a few scattering bacilli.

Two preparations from the top of each of the unlaked gravity sediments showed:

First specimen: 1 large clump and 2 single bacilli in each of the two preparations.
Second specimen: no bacilli in either slide.

Two preparations from the bottom of each of the unlaked gravity sediments showed no bacilli in any of the four slides.

In the examinations of the positive blood from the inoculated Cow 3 and of the blood to which bacilli had been added, the method of searching the sediment after laking and centrifugalizing proved very much more effective than the study of unlaked gravity sediment. Apparently the tubercle bacilli settled more slowly than blood corpuscles, with the result that the few bacilli found in the gravity sediments were in the top layers. A series of test-tubes of laked blood and another of unlaked blood-mixture were inoculated. Spreads from their gravity sediments showed many more bacilli in the preparations from the laked specimens than in those from the unlaked. It was also observed that many more scattered bacilli and small clumps were found in the top of the unlaked sediment than in the bottom. No such difference was noticed in the number of very large clumps in the top and bottom. When one considers that laking reduces the amount of sediment to a mere film, while the unlaked sediment is usually over one-fifth of the total volume of the blood-citrate

mixture after twenty-four hours of sedimentation, it is not surprising that laking greatly increases the chance of finding organisms.

Dr. Haring and I are indebted to Miss Margaret Henderson, B.S., Instructor in Bacteriology in the University of California; to Walter E. Bates, M.D., of Davis Cal.; to Archibald R. Ward, B.S.A., D.V.M., Assistant Professor of Bacteriology in the University of California; to David N. Morgan, B.S., and to Ned D. Baker, B.S., for valuable advice and assistance.

BRIEF NOTES ON THE TUBERCULOUS ANIMALS OF GROUP A

Cow 1.—Ten years old. Poor condition. Discharging sinus in right temple. Tubercle bacilli not found in the discharge. Condemned after tuberculin test in 1908. Alive Dec. 1, 1909.

Cow 2.—Nine years old. Emaciated. Condemned on account of tuberculosis in 1908. Slaughtered Oct. 23, 1909. Posterior mediastinal lymph-node caseous and calcareous. Lesion in lung 5 cm. in diameter, caseous and calcareous.

Cow 3.—Eight years old. Poor condition. Large tuberculous abscess in left axilla. Crepitation and lameness in left hip joint. This animal was used in the inoculation experiments. Died Aug. 24, 1909. Autopsy (already described) showed extensive chronic lesions of tuberculosis in the lungs and lymph-nodes.

Cow 4.—Seven years old. Fair condition. Slaughtered Aug. 25, 1909. Old tuberculous lesions in apex of right lung.

Cow 5.—About 7 years old. Fair condition. Occasional cough. Slaughtered Aug. 25, 1909. Scattered tubercles in both lungs. Caseous focus in left lung. Mediastinal lymph-nodes involved. One tubercle 2 cm. in diameter in surface of liver.

Cow 6.—Six years old. Condemned on account of tuberculosis in 1908. Well nourished at time of blood examination. Coughed frequently. Râles in lungs. Lost weight during October. Slaughtered Oct. 28, 1909. Extensive tuberculous lesions of lungs and mediastinal lymph-nodes.

Cow 7.—Six years old. Very poor condition. Large tuberculous submaxillary abscesses on both sides interfering with breathing. Frequent cough. This animal was used in the inoculation experiments. Died Sept. 15, 1909. The autopsy (already described) showed very extensive involvement of lymph-nodes and lungs.

Cow 8.—About 7 years old. Fair condition. Slaughtered Aug. 25, 1909. Left bronchial lymph-node enlarged and caseous. One posterior mediastinal lymph-node enlarged with a tubercle in the center. Foul-smelling abscess of liver (probably not tuberculous). Middle lobe of right lung solidified (also probably not tuberculous). Several pieces of wire found imbedded in stomach wall.

Cow 9.—Five years old. Good condition. Slaughtered Aug. 25, 1909. Right and left posterior pharyngeal glands caseous.

POST-MORTEM EXAMINATION OF THE THREE-YEAR-OLD ANIMALS OF GROUP B

Steer 12.—Slaughtered with the other animals of group B on Aug. 25, 1909. Right precrural lymph-node caseous.

Steer 16.—Fair condition. No definite lesions of tuberculosis found in rapid search. The animal had been tested with tuberculin a few days before being

killed. Hyperemic lymph-nodes. Minute hemorrhages in posterior pharyngeal lymph-node.

Cow 17.—Poor condition. Caseous lesions and many scattered tubercles in right lung. A few tubercles in the left. Mediastinal glands caseous and enlarged.

Steer 19.—Excellent condition. No tuberculous lesions found in rapid search.

Steer 23.—Good condition. Anterior mediastinal and left bronchial lymph-nodes caseous.

Steer 26.—Fair condition. Mesenteric lymph-nodes caseous.

Steer 27.—Good condition. Right submaxillary and the mediastinal lymph-nodes caseous and calcareous. One mesenteric and the hepatic lymph-nodes caseous. Few caseous lesions in lungs.

Steer 30.—Good condition. Had been tested with tuberculin a few days before slaughter. No unquestioned tuberculous lesions found. Minute hemorrhages in mesenteric and left bronchial lymph-nodes.

Steer 38.—Good condition. Posterior and anterior mediastinal lymph-nodes enlarged and caseous.

Steer 43.—Good condition. Few tubercles in lungs. Left bronchial and anterior and posterior mediastinal lymph-nodes caseous.

Steer 44.—Fair condition. (Had had frequent cough and râles in lungs.) Both lungs extensively involved. Mediastinal lymph-nodes calcareous. Crural lymph-nodes affected. Tubercles in liver. One tubercle 1 cm. in diameter in muscle of left ventricle of heart.

Steer 51.—Excellent condition. Anterior and posterior mediastinal and portal lymph-nodes caseous.

CONCLUSIONS

1. In 167 preparations made from the blood of 39 bleedings from 21 tuberculous cattle no tubercle bacilli were found in 110.9 hours' search; 133 of the specimens, made from gravity sediments of blood-citrate mixture, were searched 88.9 hours; the remaining 34 slides, made from laked and centrifugalized blood, were searched 22 hours.

2. In one instance tubercle bacilli were recovered by both methods of examination from blood drawn twenty-five minutes after inoculation of the arterial blood-stream.

3. Guinea-pig inoculations with the blood sediments of twenty tuberculous cattle failed to produce tuberculosis.

4. In experiments in which tubercle bacilli had been introduced into blood, either in the circulation or in test-tubes, the examination of laked and centrifugalized blood proved much more effective in the detection of the organisms than did the search of gravity sediments from unlaked mixtures of blood and citrate solution.

5. The upper portions of gravity sediment from mixtures of blood and citrate solution are much more apt to contain bacilli than the lower parts.

6. Tubercle bacilli which have been experimentally thrown into the blood-stream are rapidly removed from the circulation. Experiment suggests that the capillaries of the lungs are more efficient in arresting bacilli than the peripheral capillaries.

7. Chronic tuberculosis may produce a marked partial immunity against fresh inoculation with tubercle bacilli.

2434 Durant Avenue.

EDITOR'S NOTE

In the paper by Drs. Marine and Lenhart on the "Relation of Iodin to the Structure of Human Thyroids," in THE ARCHIVES for November, 1909, on page 487, lines 17-16 from the bottom, occur the words, in parenthesis, "2 to 5 grams daily." This should read "2 to 5 grains three times daily."

INDEX TO VOLUME IV

PAGE.

Bachmann, George: Sphygmographic Study of Complete Heart-block..... 238
Barker, Lewellys, F., and Hirschfelder, A. D.: Effects of Cutting the Branch of the His Bundle Going to the Left Ventricle..... 198
Barringer, Theodore B.: Stokes-Adams' Disease..... 186
Bile Salts, Ulceration of the Stomach and Necrosis of Salivary Glands Resulting from Experimental Injection of; A. W. Sellards..... 502
Billings, Frank: Chronic Infectious Endocarditis..... 409
Blastomycosis, Systemic; B. W. Fontaine, M. Haase, R. H. Mitchell..... 101
Book Reviews; Sahli, 191; von Jürgensen, Krehl and von Schrotter..... 97
Burns, J. Edward: Glandular Fever..... 118

Chamberlain, Weston P.: Uncinariasis in the United States Army..... 8
Cotton, W. E., and Schroeder, E. C.: Tubercle Bacilli in the Circulating Blood..... 133
Coleman, Warren, and Shaffer, P. A.: Protein Metabolism in Typhoid..... 538

Darling, Samuel T.: Relapsing Fever of Panama..... 150
Davis, David J.: Influenzal Meningitis..... 323
Diagnostic Methods of Examination, A Treatise on by Sahli; a review of... 191
Digestion, Gastric, Observations on in a Child with Gastric Fistula; R. S. Lavenson..... 271

Edema, Experimental Acute Pulmonary, Mechanical Factors in; J. L. Miller and S. A. Matthews..... 356
Endocarditis, Chronic Infectious; F. Billings..... 409
Ewing, James, and Wolf, C. G. L.: Clinical Significance of the Urinary Nitrogen..... 330

Fever, Glandular; J. E. Burns..... 118
Fever, Relapsing, of Panama; S. T. Darling..... 150
Fontaine, Bryce W., Haase, M., and Mitchell, R. H.; Systemic Blastomycosis. 101
Fox, Herbert, and White, C. Y.: Tuberculin Tests in Monkeys..... 517
Friedman, J. C.: Modified Sahli Butyrometric Test Meal..... 69
Frothingham, Channing: Effect of Hexamethylenamin on Guinea-Pigs..... 510
Gonococcemia; E. E. Irons..... 601

Greer, James R., and Wells, H. G.: Absence of Adrenalin in Malignant Renal Hypernephromas..... 291

Haase, Marcus, Fontaine, B. W., and Mitchell, R. H.: Systemic Blastomycosis..... 101
Heart-Block, Complete, Sphygmographic Study of; G. Bachmann..... 238
Heart, Diseases of by T. von Jürgensen, L. Krehl, and L. von Schrotter; review of..... 97
Heart Sound, the Third; W. S. Thayer..... 297

PAGE.

Herb, Isabella C.: Experimental Parotitis 201
Hexamethylenamin, Effect of on Guinea-Pigs; C. Frothingham 510
Hirschfelder, A. D., and Barker, L. F.: Effects of Cutting the Branch of the His Bundle Going to the Left Ventricle 198
His Bundle Going to Left Ventricle, Effects of Cutting the Branch of; L. F. Barker and A. D. Hirschfelder 198
Hiss, Philip Hansen: Immunity and the Treatment of Infectious Diseases 32
Hypernephromas, Absence of Adrenalin in Malignant Renal; J. R. Greer and H. G. Wells 291

Immunity and the Treatment of Infectious Diseases; P. H. Hiss 32
Immunity, Relation of Hypersusceptibility to; P. A. Lewis 528
Insanity, Much-Holzmann Serum Reaction in; A. J. Rosanoff 405
Iodin and Thyroid; see Thyroid .....
Irons, Ernest E.: Gonococcemia 601

Von Jürgensen's Diseases of the Heart; review of 97

Kolmer, John Albert: Blood in Pertussis 81
Krehl's Diseases of the Heart; review of 97
Lavenson, R. S.: Gastric Digestion Observed in a Child with Gastric Fistula. 271
Lenhart, C. H., and Marine, D.: Effects of Iodin-Containing Compounds in Thyroids of Dogs 253
Lenhart, C. H., and Marine, D.: Relation of Iodin to the Structure of Human Thyroids 440
Lewis, Paul A.: Relation of Hypersusceptibility to Immunity 528
Lymphatic Apparatus, Unusual Lesions of; D. Symmers 218
Lyons, Randolph: Clot Culture and Agglutination Test in Typhoid 64

Marine, David, and Lenhart, C. H.: Effect of Iodin-Containing Compounds in Thyroids of Dogs 253
Marine, David, and Lenhart, C. H.: Relation of Iodin to the Structure of Human Thyroids 440
Matthews, S. A., and Miller, J. L.: Mechanical Factors in Experimental Acute Pulmonary Edema 356
Meningitis, Influenzal: D. J. Davis 323
Miller, E. C. L.: The Adminstration of Tuberculin 126
Miller, Joseph L., and Matthews, S. A.: Mechanical Factors in Experimental Acute Pulmonary Edema 356
Mitchell, Robert H., Fontaine, B. W., and Haase, M.: Systemic Blastomycosis 101

Nitrogen, Urinary, Clinical, Significance of; Nitrogenous Metabolism in Typhoid; J. Ewing and C. G. L. Wolf 330

Parotitis, Experimental; I. C. Herb 201
Peabody, Francis W.: Venous Pulse in Paroxysmal Tachycardia 432
Pertussis, Blood in; J. A. Kolmer 81
Pottenger, F. M.: Effect of Tuberculosis on the Heart 306

PAGE.

Rosanoff, A. J.: Much-Holzmann Serum Reaction in Insanity 405

Sahli's Treatise on Diagnostic Methods of Examination; review of 191
Sawyer, Wilbur A.: Tubercle Bacilli in the Blood 628
Schroeder, E. C., and Cotton, W. E.: Tubercle Bacilli in the Circulating Blood 133
Von Schrotter's Diseases of the Heart; review of 97
Sellards, Andrew Watson: Experimental Injection of Bile Salts 502
Shaffer, Philip A., and Coleman, W.: Protein Metabolism in Typhoid 538
Stokes-Adams' Disease; T. B. Barringer 186
Swift, Homer F.: Comparative Study of Serum Diagnosis in Syphilis 376
Swift, Homer F.: Complement Deviation Test for Syphilis 494
Symmers, Douglas: Lesions of the Lymphatic Apparatus 218
Syphilis, Use of Active and Inactive Serum in Complement Deviation Test for; H. F. Swift 494
Syphilis, Serum Diagnosis in; H. F. Swift 376

Tachycardia, Paroxysmal, Venous Pulse in; F. W. Peabody 432
Test Meal, A Modification of the Sahli Butyrometric; J. C. Friedman 69
Thayer, William Sydney: The Third Heart Sound 297
Thyroids, Human, Relation of Iodin to the Structure of; D. Marine and C. H. Lenhart 440
Thyroids of Dogs, Normal, Colloid or Actively Hyperplastic (Parenchymatous), Effects of Adminstration or Withholding of Iodin-Containing Compounds on; D. Marine and C. H. Lenhart 253
Tileston, Wilder: Disseminated Miliary Tuberculosis of the Skin 21
Tubercle Bacilli in Circulating Blood; E. C. Schroeder and W. E. Cotton 133
Tubercle Bacilli in the Blood; W. A. Sawyer 628
Tuberculin, Administration of; E. C. L. Miller 126
Tuberculin Tests in Monkeys; C. Y. White and H. Fox 517
Tuberculosis, Effect of, on the Heart; F. M. Pottenger 306
Tuberculosis of the Skin, Disseminated Miliary; W. Tileston 21
Tuberculosis, Pulmonary, Hyperalgesia of Skin Overlying Active Lesions in; W. C. White and K. H. Van Norman 1
Typhoid, Clot Culture and Agglutination Test in; R. Lyons 64
Typhoid, Protein Metabolism in; P. A. Shaffer and W. Coleman 538

Uncinariasis Among Apparently Healthy Southern-Bred White Men in the United States Army; Weston P. Chamberlain 8

Van Norman, Karl H., and White, W. C.: Hyperalgesia of the Skin Overlying Active Lesions in Pulmonary Tuberculosis 1

Wells, H. Gideon, and Greer, J. R.: Absence of Adrenalin in Malignant Renal Hypernephromas 291
White, C. Y., and Fox, H.: Tuberculin Tests in Monkeys 517
White, Wm. C., and Van Norman, K. H.: Hyperalgesia of the Skin Overlying Active Lesions in Pulmonary Tuberculosis 1
Wolf, C. G. L., and Ewing, J.: Clinical Significance of the Urinary Nitrogen. 330

GENERAL LIBRARY
UNIV. OF MICH.
DEC 24 1909

VOLUME 4 NUMBER 6

THE ARCHIVES OF INTERNAL MEDICINE

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago

RICHARD C. CABOT, Boston GEORGE DOCK, New Orleans, La.

DAVID L. EDSALL, Philadelphia THEO. C. JANEWAY, New York City

W. S. THAYER, Baltimore

DECEMBER 15, 1909

CHICAGO
AMERICAN MEDICAL ASSOCIATION
PUBLISHERS

Entered as Second-Class Matter, January 22, 1908, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879.

CONTENTS OF NUMBER 1, VOLUME 4

PAGE.

Studies of the Serum Globulin, Albumin Ratio in Pulmonary Tuberculosis. William G[illespie] Thom, M.D., and Karl H. Van Norman, M.B. (Tor.), Fitchburg, Mass. 1

Prevalence and Importance of Orthopædic Affections Among Apparently Southern-born Negroes in the United States Army. Hunter P. Chamberlaine, M.D., Jackson Barracks, La. 6

Generalized Miliary Tuberculosis of the Skin. An Infrequent Sign in General Miliary Tuberculosis. William Thalhimer, M.D., Chicago 21

Progress in Immunity: [illegible] Treatment of Infectious Diseases. Wilson Hanson Hiss, Jr., M.D., Boston 32

Blood Culture in Consumption: Their Absolute Value; Test in Typhoid. Randolph Lyons, M.D., New Orleans 46

Examination of the Sarcina Ventriculi in Test Meal. J. C. Einhorn, M.D., Chicago 60

Count of the Blood in Pneumonia. Albert Robin, M.D., Paris, France. 61

Diseases of the Heart. Von Noorden, Ewald, Von Leyden 97

CONTENTS OF NUMBER 2, VOLUME 4

Rose Plant-mycosis. [illegible] Bruce W. Hollis, M.D., Hugo Haase, M.D., and [illegible] Mobile, Ala. 101

Malarial Fever. Report of Cases Occurring in the [illegible] Wards of the Union Protestant Infirmary. J. Edward Young, M.D., Baltimore 110

Administration of Tuberculin. R. C. M. Page, M.D., Baltimore 126

Concerning Tuberculin Reaction and the Circulating Blood. E. C. Fussell and W. E. Cotton, Philadelphia, Pa. 133

Relapsing Fever of Panama. [illegible] Darling, M.D., Ancon, Canal Zone 150

Report of a Case of Stokes-Adams Disease. Theodore B. Hyslop, M.D., New York 158

Relative Diagnostic Importance of Examination. [illegible] Different Organs 191

CONTENTS

PAGE

I. Results of Tuberculin Tests in Monkeys at the Philadelphia Zoological Gardens. C. Y. White, M.D., and Herbert Fox, M.D., Philadelphia..... 517

II. The Relation of Hypersusceptibility to Immunity. Paul A. Lewis, M.D., New York..... 529

III. Protean Metabolism in Typhoid Fever. Philip A. Shaffer, Ph.D., and Warren Coleman, M.D., with the Assistance of Michael Somogyi, E. A. Erlanger and Edna Cutler, New York..... 538

IV. Gonococcemia, with a Report of Six Cases in which the Gonococcus Was Isolated from the Blood During Life. Herbert E. Irons, M.D., Chicago..... 601

V. Tubercle Bacilli in the Blood. Wilbur A. Sawyer, M.D., Berkeley, Cal..... 628

The Archives of Internal Medicine is issued monthly. Two volumes are published annually, each of about 650 pages.

Manuscripts offered for publication and other correspondence relating to the editorial management of The Archives should be sent to Dr. Joseph L. Miller, 100 State Street, Chicago. Communications regarding subscriptions, reprints, etc., should be addressed to The Archives of Internal Medicine, American Medical Association, 535 Dearborn Avenue, Chicago.

Footnotes and bibliographies should conform to the style of the Index Medicus or to that of the Index-Catalogue of the Surgeon-General's Library. It is specially requested that the titles of articles and the exact date of issues, year, volume and page, be given in each case. Contributors are requested not to furnish bibliographies which are unnecessary, or mere clerical compilations. On receipt of 10 cents the American Medical Association will send a pamphlet entitled "Bibliographic Style," containing suggestions to authors on the preparation of manuscripts, rules for footnotes and bibliographies and a list of several hundred medical periodicals of the world with approved abbreviations of each.

Authors will receive two hundred and fifty reprints free; additional copies may be obtained at cost.

The subscription price is $4.00 (16 shillings, 18 marks, 22 francs, including postage) per annum of two volumes. Single copies, 50 cents.

Make checks etc., payable to the AMERICAN MEDICAL ASSOCIATION.

CONTENTS OF [illegible] VOLUME 4

[illegible]

CONTENTS OF [illegible] VOLUME 4

[illegible]

CONTENTS OF [illegible] VOLUME 4

[illegible]